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Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.01/A1

Topic: A.07. Developmental Disorders

Title: Identification of druggable gene coexpression networks driving PWS, CCHS, and ROHHAD in human dental pulp stem cells

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[1]Dept. of Chem. Sci., Crescent University, Abeokuta, Abeokuta, Nigeria; [2]Dept. of Chem. Sci., CRESCENT UNIVERSITY, Abeokuta, Nigeria

Abstract: Prader-Willi syndrome (PWS), congenital central hypoventilation syndrome (CCHS), and Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome are rare neurodevelopmental disorders with overlapping clinical features, yet their underlying molecular mechanisms are still poorly understood. This study seeks to unravel the intricate coexpression networks driving the pathogenesis of these syndromes, aiming to identify biomarkers and therapeutic targets for novel pharmacotherapeutic interventions. CCHS and ROHHAD transcriptomics dataset (GSE216125) and PWS conferred by uniparental disomy versus deletion (GSE178687) from dental pulp stem cells from neurotypical control, PWS, ROHHAD, and CCHS subjects differentiated into neuronal cultures followed by RNA sequencing were pooled for a weighted gene coexpression (WGCNA) network analysis to reveal common dysregulated biomarkers. Data quality was checked for batch effect and correction, and outlier samples were removed after hierarchical clustering and principal component analysis. We then constructed a co-expression network to identify modules and examine module-trait relationships via correlation-level plot. Driver genes within modules were identified, and their gene significance was elucidated. These were exported into cytoscape software to obtain hub genes driving disease pathogenesis. Pathways enrichment analysis of the gene set was elucidated followed by druggability analysis. Our robust exploration revealed common dysregulation of CCT7, COA6, COX4I1, COX5A, COX6A1, COX6B1, COX8A, CYCS, HUWE1, KPNB1, MDH2, NDUFS6, NFKBIA, NUDC, PSMA4, PSMC3, PSMC4, PSMC5, PSMD1, PSMD11, PSMD14, PSMD4, SLC25A5, and UQCRC1 in the blue module in PWS, CCHS and ROHHAD. Pathway enrichment analysis revealed these changes significantly impacted cellular response and signaling pathways, cell cycle regulation and checkpoints, DNA replication and repair, protein degradation and modification, and immune system response. Gene ontology analysis demonstrated common global impact of PWS, CCHS, and ROHHAD on mitochondrial components and processes and transmembrane transporter activities. These hub genes present as clinically actionable cell surfaces, enzymes, and druggable genomes. This study extends our understanding of the molecular overlap among ROHHAD, CCHS, and PWS. Developing novel therapeutic modulators of these druggable targets holds implications for care packages to alleviate suffering in people presenting with PWS, CCHS and ROHHAD.

Disclosures: O. Taofeek: None. **O. Oyewole:** None. **Y. Salami:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.02/A2

Topic: A.07. Developmental Disorders

Title: Exploring translational opportunities through phenotypic characterization in a mouse model of Angelman syndrome

Authors: *J. ZYUZIN[1], M. S. TRUJILLO[2], E. GONZALO GIL[3], L. CASE[3];
[1]The Jackson Lab., Los Angeles, CA; [2]Jax Mice and Clin. Services, The Jackson Lab., Sacramento, CA; [3]The Jackson Lab., Bar Harbor, ME

Abstract: Angelman Syndrome is a rare neuro-genetic disorder, occurring in approximately 1 in 10,000 to 20,000 live births, and is associated with deletions or mutations in the maternally inherited ubiquitin ligase E3A (UBE3A) gene.
Angelman syndrome leads to delays in speech, balance and cognitive development, and there is a critical need for effective therapeutic interventions. There is no known effective therapeutic or prophylactic treatment that eliminates all symptoms of Angelman Syndrome. Genetically modified mouse models are essential pre-clinical tools for assessing the safety and efficacy of gene therapies and small molecule therapeutics in curing or alleviating debilitating symptoms of the disease.
This natural history study underscores the importance of a murine model of Angelman Syndrome, heterozygous for the maternally-inherited Ube3a-null allele, in translational research. The mouse model for Angelman Syndrome (JAX Stock#016590) displays decreased electroconvulsive threshold ($p<0.05$), demonstrating increased susceptibility for seizures. Additionally, these mice show impairments in nest building ($p<0.05$), suggesting impairments in fine motor control. Furthermore, gross motor control is impaired as measured by locomotion (open field; $p<0.05$), motor coordination (rotarod; $p<0.05$), and gait dynamics (gait analysis; $p<0.01$). This model exhibits significant parallels with the clinical disease phenotype of patients with Angelman Syndrome.
Similarly, to previous findings, this natural history study further emphasizes the importance of Ube3a-null “B6 AS” mouse model of Angelman Syndrome and it demonstrates predictable and reproducible phenotypes and may be a useful platform for assessing potential therapeutics aimed at curing or treating this disease, and for advancing our understanding of Angelman Syndrome pathophysiology. The model's fidelity in recapitulating clinical phenotypes presents an excellent tool for preclinical investigations of Angelman Syndrome pathology and potential interventions.

Disclosures: J. Zyuzin: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M.S. Trujillo:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **E. Gonzalo**

Gil: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **L. Case:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.03/A3

Topic: A.07. Developmental Disorders

Title: Novel Subtypes of Infantile Prader-Willi Syndrome using Brain Connectivity on Overnight Polysomnography

Authors: *W. KIM[1], **S. KIM**[2];
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Abstract: Objective Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by hypotonia and feeding difficulties in infancy, growth hormone deficiency, hypogonadism, behavioral problems, cognitive impairment, hyperphagia leading to obesity, and a high prevalence of obstructive sleep apnea syndrome (OSAS) in early childhood. Although there had been many studies on genetic subtyping of PWS, there is still no subtyping study in terms of sleep disorders. The authors conducted this preliminary study to identify new subtypes based on the brain connectivity shown in overnight polysomnography (PSG) in infantile PWS before growth hormone therapy. **Methods** The 6-channel sleep electroencephalography (EEG) and PSG parameters of infantile PWS patients who were evaluated for OSAS was collected. Imaginary coherence between each channel is calculated for each frequency band (delta [0.5-4.0 Hz], theta [4.0-8.0 Hz], alpha [8.0-12.0 Hz], sigma [12.0-16.0 Hz], beta [16.0-30.0 Hz], gamma [30.0-50.0 Hz]). Average clustering coefficient of EEG data was calculated through graph theory analysis after principal component analysis (PCA), and then k-means clustering was performed. **Result** Total of 7 patients were included for the analysis. Median age was 5 months old (3-9 months). Median body mass index 14.8 (12.4 - 16.7). All patients had hypotonia and global developmental delay. Median obstructive apnea hypopnea index (AHI) was 0 (range 0 - 0.9) and median central AHI was 1.5 (range 0-7.4). K-means clustering was conducted using 2 principal components from 6 variables. The 2 clusters model showed the best average silhouette index (0.24). There was no difference in PSG parameters between the two groups. **Conclusion** In this preliminary study, we found two subtypes in infantile PWS population through graph theory analysis of 6-channel sleep EEG. Follow up of PSG parameters and neurodevelopmental outcome is warranted for further study.

Disclosures: W. Kim: None. **S. Kim:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.04/A4

Topic: A.07. Developmental Disorders

Support: Angleman Syndrome Foundation Pilot Award
NIH F32NS131217

Title: Causally linking UBE3A misexpression to altered circuit dynamics controlling skilled movements

Authors: *S. M. LEMKE, *J.-Z. GUO, M. C. JUDSON, B. D. PHILPOT, A. W. HANTMAN; Cell Biol. and Physiology, Neurosci. Ctr., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Misregulation of the 15q11-q13 chromosomal region is particularly consequential for neurodevelopment. Maternal copy number increases in 15q11-q13 cause duplication 15q (Dup15q) syndrome, a major subtype of autism spectrum disorder, while maternal (but not paternal) 15q11-q13 deletions cause the neurodevelopmental disorder Angelman syndrome (AS). There are ~20 genes in the 15q11-q13 region, but only UBE3A is expressed exclusively from the maternal allele in mature neurons, hence it is thought to be the main genetic driver for AS and Dup15q syndrome. Motor deficits are among the earliest and most impactful clinical phenotypes in AS and Dup15q syndrome, although the precise manifestation differs by disorder. We currently lack an understanding of how UBE3A misexpression alters neural circuit dynamics to impair movement control. Here we test the central hypothesis that the motor phenotypes resulting from UBE3A misexpression are caused by altered dynamics in specific neural circuits. We use mouse models to identify the impact of varying UBE3A levels on motor brain networks during the acquisition and production of a skilled reach-to-grasp movement that requires planning, action sequencing, sensory-guided corrections, and adaptation. Our goal is to identify rules that govern the complex relationship between Ube3a gene dosage, motor deficits, and distributed brain network formation and function. Finally, we test a translationally relevant gene therapy to correct UBE3A levels in relevant motor circuits and restore typical motor function. This work will (1) establish the impact of UBE3A level on skilled movements, (2) establish the impact of UBE3A level on brain-wide neuronal dynamics, and (3) causally link circuit-specific UBE3A normalization to neural dynamics and skilled movements. The ultimate goal of this work it to help develop safe and efficacious therapeutic approaches for ameliorating motor deficits in Angelman and Dup15q syndromes.

Disclosures: S.M. Lemke: None. **J. Guo:** None. **M.C. Judson:** None. **B.D. Philpot:** None. **A.W. Hantman:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.05/A5

Topic: A.07. Developmental Disorders

Title: Characterization of the Ube3a mouse model of Angelman Syndrome in neonates and adults

Authors: *J. GRESACK, A. GHAVAMI, S. RAMBOZ;
PsychoGenics, Paramus, NJ

Abstract: Angelman Syndrome (AS) is a rare genetic neurodevelopmental disorder characterized, in part, by developmental delays, movement impairments, and difficulties with communication and language, the effects of which impact children and adults living with AS. The B6.129S7-Ube3atm1Alb/J (B6-E6-AP) mouse line displays characteristics of Angelman syndrome (AS) by knocking out the Ube3a allele in neurons. Here we characterized the phenotypic profile of this model by assessing behavioral performance in both neonatal and adult Ube3a heterozygous gender mixed mice (wild-type litter mates served as controls). Animals were tested in a battery of behavioral tests starting at birth, including assessments for geotaxis, righting reflex and ultrasonic vocalizations (USV) which Ube3a heterozygous animals exhibited abnormalities. In adulthood, animals were again evaluated for ultrasonic vocalizations in addition to being tested in a battery of motor paradigms including open field and grip strength. Decreases in the diversity and complexity of the USV repertoire were observed in Ube3a heterozygous animals in adulthood. Adult Ube3a heterozygous animals also exhibited decreased grip strength, decreased distance traveled and rearing frequency in the open field. PsychoGenics' AI-enabled cube technologies were also used showing disrupted gait as compared to wild-type littermates. Evaluation of protein markers in the Ube3a mouse are in progress and results are pending. The ultimate goal of this work is to identify robust early onset and non-invasive readouts that can be used to determine the efficacy of disease modifying therapies for Angelman Syndrome.

Disclosures: J. Gresack: None. **A. Ghavami:** None. **S. Ramboz:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.06/A6

Topic: A.07. Developmental Disorders

Support: NIH grant R21MH134184

Title: The roles of the neurodevelopmental disease-linked protein Ube3a in Golgi satellite function

Authors: U. J. RODRIGUEZ[1], *T. A. RUSSELL[2], S. KNACK[1], O. JEYIFOUS[1], W. N. GREEN[1];
[1]Neurobio., Univ. of Chicago, CHICAGO, IL; [2]Univ. of Chicago, CHICAGO, IL

Abstract: The UBE3A gene is strongly associated with neurodevelopmental disorders, with variants that decrease or increase UBE3A protein expression and function linked to Angelman syndrome and autism spectrum disorder, respectively. The Ube3a protein is a ubiquitin ligase expressed in the nucleus and cytosol involved in the targeting of various proteins for proteosomal degradation, and also acts as a co-activator of gene transcription. In neurons, Ube3a also localizes to the Golgi apparatus (GA), and loss of its expression alters GA morphology, acidification, and the addition of sialic acid to glycosylated proteins. We have begun to address whether Ube3a has a similar role with regard to Golgi satellites (GSats), small mobile organelles found in the soma and neurites whose numbers are regulated by neuronal activity. Like the GA, GSats are acidic and contain Golgi enzymes needed for complex processing of glycans. In primary cortical cultures, we find that with a long-term rise in synaptic activity, dendritic Ube3a becomes highly colocalized with GSats. Neuronal stimulation also increases the number of dendritic GSats, but shRNA-mediated knockdown of Ube3a blocks this increase. Additionally, increasing neuronal activity leads to higher levels of the binding of lectins that specifically recognize sialic acid on dendritic spine heads. Knocking down total Ube3a protein or overexpressing individual UBE3A splice variant isoforms appears to interfere with this activity-dependent glycosylation. Taken together, our data reveal novel functions for Ube3a in regulating synapse features and provide new insights into the pathophysiological mechanisms underlying UBE3A-linked neurodevelopmental disorders.

Disclosures: U.J. Rodriguez: None. **T.A. Russell:** None. **S. Knack:** None. **O. Jeyifous:** None. **W.N. Green:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.07/A7

Topic: A.07. Developmental Disorders

Title: Development of an iPSC-based functional validation platform for Dup15q Syndrome

Authors: P. ZHOU[1], A. MURCHISON[1], M. NICHOLSON[2], A. M. MAROOF[1], B. TORROBA[3], D. F. FISCHER[4], R. REDIS[3], W. W. POON[5], D. LESSARD[1], **P. MITCHELL**[6], *D. MAGNANI[7];
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Abstract: Maternal 15q duplication syndrome (Dup15q) is a rare neurodevelopmental disorder caused by the presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR). This region ~5 Mb long is located within 15q11.2-q13.3 chromosome region. Individuals with maternal Dup15q syndrome exhibit a wide spectrum of clinical symptoms including hypotonia and motor delays, variable intellectual disability, autism spectrum disorder and epilepsy. Although over 40 genes map to the PWACR, accumulating data implicate ubiquitin-protein E3A ligase (*UBE3A*) overexpression as the predominant mechanism. Therefore, the lowering of UBE3A expression by antisense oligonucleotides (ASOs) might be able to reduce the severity of the symptoms. We embarked on a ASO discovery program to identify and characterize non-allele specific ASO candidates targeting UBE3A transcripts for a single Dup15q patient. Upon an initial screening of 200 sequences in control human fibroblasts, three ASO candidates have been selected based on in vitro safe profiles by PBMC immunotoxicity assays, their robust UBE3A knockdown efficacy at mRNA and protein levels in Dup15q iPSC-derived cortical neurons and good tolerability in rodents. Here, we describe the ongoing proof-of-concept studies focused on characterizing the neuronal electrophysiological properties of Dup15q patient neurons and isogenic control (loss of dup15q) using Microelectrode Arrays (MEAs). We have generated iPSC-derived glutamatergic and GABAergic neurons from a Dup15q patient and isogenic control. Preliminary results show that while Dup15q does not affect global neuronal maturation, significant differences in parameters associated with glutamatergic neuron hyperexcitability have been identified. These results are consistent with previous studies and nominate MEA-based readouts for establishing functional validation assays for therapeutic candidates to treat Dup15q patients. Ongoing studies are focused on ASO phenotype rescue for lead selection.

Disclosures: P. Zhou: None. **A. Murchison:** None. **M. Nicholson:** None. **A.M. Maroof:** None. **B. Torroba:** None. **D.F. Fischer:** None. **R. Redis:** None. **W.W. Poon:** None. **D. Lessard:** None. **P. Mitchell:** None. **D. Magnani:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

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Topic: A.07. Developmental Disorders

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Title: Fetal brain-derived exosomal miRNAs from maternal blood: Potential diagnostic biomarkers for fetal alcohol spectrum disorders

Authors: *M. SELZER[1,2,3], M. HAMPE[4], D. MARTIROSYAN[4], A. BAJWA[4], A. DARBINYAN[5], N. MERABOVA[4,6], G. TATEVOSIAN[4], L. GOETZL[7], S. AMINI[8], N. DARBINIAN[4];
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Abstract: Introduction. Fetal alcohol spectrum disorders (FASD) are leading causes of neurodevelopmental disability, but they cannot be diagnosed early *in utero*. Because several microRNAs (miRNAs) are implicated in other neurological and neurodevelopmental disorders, the effects of EtOH exposure on expression of these miRNAs and their target genes and pathways were assessed. **Methods.** In women who drank alcohol (EtOH) during pregnancy and non-drinking controls matched individually for fetal sex and gestational age, the levels of miRNAs in fetal brain-derived exosomes (FB-Es) isolated from the mothers' serum correlated well with the contents of corresponding fetal brain tissues obtained after voluntary pregnancy termination. In 6 EtOH-exposed cases and 6 matched controls, levels of fetal brain and maternal serum miRs were quantified on the array by qRT-PCR. In FB-Es from 10 EtOH-exposed cases and 10 controls, selected miRNAs were quantified by ddPCR. Protein levels were quantified by ELISA. **Results.** There were significant EtOH-associated reductions in expression of several miRNAs, including miR-9 and its downstream neuronal targets BDNF, REST, synapsin and sonic hedgehog. In 20 paired cases, reductions in FB-E miR-9 levels correlated strongly with reductions in fetal eye diameter, a prominent feature of FASD. **Conclusions.** FB-E miR-9 levels might serve as a biomarker to predict FASD in at-risk fetuses. The results also could suggest therapeutic approaches to preventing or ameliorating FASD.

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Poster

PSTR099: Angelman and Other Developmental Disorders

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Program #/Poster #: PSTR099.09/A9

Topic: A.07. Developmental Disorders

Support: RTW Charitable Foundation
NIH R01MH124808
NIH T32NS121881

Title: Developing RNA therapeutics for restoring gene function in MYT1L neurodevelopmental disorder

Authors: *M. A. GACHECHILADZE[1], A. D. FISCHER[1], R. PRAKASAM[2], B. D. BOROS[1], T. M. MILLER[3], K. L. KROLL[1], J. D. DOUGHERTY[4];
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Abstract: Therapeutic restoration of protein function is a key goal for many neurodevelopmental disorders (NDDs) caused by genetic haploinsufficiency. *MYT1L* syndrome is a recently identified, understudied NDD caused by heterozygous mutations in the *MYT1L* gene, characterized by global developmental delay, intellectual disability, highly penetrant obesity and hypotonia, and significant comorbidity with autism and/or attention-deficit/hyperactivity disorder (ADHD). Mice and human neurons with a *MYT1L* stop-gain mutation only show 30-50% decreased transcript and protein levels, yet display profound cellular, molecular, and behavioral anomalies, indicating that MYT1L levels need to be tightly controlled for normal function. However, it is unknown how MYT1L levels are regulated. Understanding this regulation is a key step to identifying clinically relevant strategies for upregulating MYT1L as a therapy for *MYT1L* syndrome. An emerging protein upregulation strategy is to use antisense oligonucleotides (ASOs) to block elements that normally destabilize mRNA, such as adenylate/uridylate (AU)-rich elements and binding sites of RNA-binding proteins and microRNAs. Thus, ASOs could be used to increase protein expression from the mRNA of the remaining healthy allele. Here, we took both a rational, bioinformatic approach and an unbiased, high-throughput approach to identify regions that may destabilize MYT1L transcripts. Using bioinformatic predictions and empiric binding data, we have identified several putative repressive elements. To determine the effects of these repressive elements on protein synthesis, we tested ASOs masking these elements using a dual fluorescence reporter in HEK293 cells, and discovered several promising ASO candidates that increase reporter expression. In parallel, we are using a massively parallel reporter assay (MPRA) to screen 3' untranslated region (UTR) elements for destabilizing activity in an unbiased manner. A preliminary screen in HEK293 cells has identified several potential destabilizing regions of the MYT1L 3' UTR. However, since the effects of regulatory elements are highly cell type-specific, studies in a neuronal system are ongoing to query these reagents in the endogenous regulatory milieu for MYT1L transcripts. These studies will begin to explore MYT1L post-transcriptional regulation and provide clinically relevant insights for rescue of *MYT1L* haploinsufficiency by direct ASO targeting of MYT1L mRNA.

Disclosures: M.A. Gachechiladze: None. **A.D. Fischer:** None. **R. Prakasam:** None. **B.D. Boros:** None. **T.M. Miller:** 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.; C2N, Ionis. F. Consulting Fees (e.g., advisory boards); Ionis, Biogen, Bioio, LLC, Arbor Bio. Other; Denali: honorarium. **K.L. Kroll:** None. **J.D. Dougherty:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.10/A10

Topic: A.07. Developmental Disorders

Support: Eagles Autism Foundation

Title: Characterization of PRKAR1B mutations associated with neurodegenerative and neurodevelopmental disorders

Authors: *A. GLEBOV-MCCLOUD[1], R. A. MERRILL[2], S. STRACK[3];
[2]Dept. of Mol. Physiol. and Biophysics, [1]Univ. of Iowa, Iowa City, IA; [3]Dept. of Neurosci. and Pharmacol., Univ. Iowa, Iowa City, IA

Abstract: PRKAR1B encodes the protein kinase A (PKA) regulatory R1β subunit and has been linked to both neurodegenerative and neurodevelopmental disorders (NDNDDs). Unfortunately, our understanding of the underlying mechanisms that cause NDNDDs is limited. A novel neurodegenerative disorder characterized by dementia and parkinsonism is associated with the L50R R1β mutation. The L50 residue is in R1β's dimerization/docking (D/D) domain, suggesting that the L50R mutation disrupts both R1β dimerization and R1β binding to A-kinase anchoring proteins (AKAPs), which bring PKA to specific subcellular compartments. PRKAR1B has also been linked to neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD) and Marbach-Schaaf neurodevelopmental syndrome (MASNS). Whole exome sequencing studies identified the de novo R243C R1β mutation in individuals with ASD. Moreover, the monoallelic Q167L, E196K, and R335W R1β mutations were discovered in individuals with MASNS. These mutated NDD residues are all in R1β's cyclic adenosine monophosphate (cAMP) binding regions, indicating that they disrupt PKA activation. These reports suggest that PKA is involved in both neurodegeneration and neurodevelopment. In this work, we want to determine how the R1β mutations affect PKA function. We measured changes in regulatory subunit dimerization and the interaction between PKA regulatory and catalytic subunits using both coimmunoprecipitations (co-IPs) and a NanoBiT split-luciferase assay (NanoBiT assay). We also used a luciferase reporter assay to measure changes in transcriptional activity following treatment of cells with isoproterenol. With the co-IPs and NanoBiT assay, we discovered that only L50R does not dimerize with wild-type (WT) R1β. Moreover, L50R does not colocalize with AKAP1 or small membrane AKAP. We have also shown that the L50R and MASNS mutants alter R1β's ability to bind to the PKA catalytic subunit (PKAc). Using a luciferase reporter assay, we found that, in primary neuronal cultures treated with isoproterenol, all MASNS R1β mutants notably decrease transcriptional activity compared to WT R1β. Lastly, preliminary data in primary neuronal cultures indicate that both L50R and R335W show reduced neurite outgrowth relative to neurons expressing WT R1β. These findings reveal that while both L50R and MASNS mutants disrupt normal cell signaling events, the mechanisms through which

they do so are distinct. The L50R mutant disrupts cell signaling through mislocalization of PKA, while the MASNS mutants disrupt cell signaling by altering cAMP-mediated activation of PKA.

Disclosures: A. Glebov-McCloud: None. **R.A. Merrill:** None. **S. Strack:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.11/A11

Topic: A.07. Developmental Disorders

Support: NIH NINDS R21NS136889

Title: Investigating the pathological mechanisms of PACS2 syndrome

Authors: *C. BOSSERT, A. D. GUEMEZ-GAMBOA;
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Abstract: Neurodevelopmental disorders are diverse and often present with complex etiology. Individuals with these conditions display cognitive impairment accompanied by lifelong deficits, however, little is known about their neurological basis. PACS2 syndrome is a rare developmental and epileptic encephalopathy characterized by early-onset epilepsy, facial dysmorphism, cerebellar dysgenesis, and developmental delay. Exome sequencing revealed that patients shared a *de novo* heterozygous missense variant c.625 G>A in the *pacs2* gene which results in a Glutamic acid (E) to Lysine (K) substitution in residue 209 of the PACS2 protein (p.E209K). The canonical function of PACS2 is to traffic client proteins between the endomembrane system. Literature highlights PACS2 for its roles in apoptosis and as a mitochondrial-associated membrane (MAM) protein. However, the way PACS2 p.E209K impacts these functions and the role it plays in the pathology of PACS2 syndrome is poorly understood. Overexpression studies reveal that p.E209K cortical neurons have reduced MAM formation and increased cytosolic Ca^{2+} concentrations that leads to increased neurotransmitter release. While p.E209K's effect on apoptosis has been studied in a cancer cell line, results remain inconclusive. Consequently, no studies have been done on a neuronal context and using endogenous PACS2 p.E209K expression. Therefore, to generate relevant cell models, we used CRISPR-Cas9 to establish 2 pairs of isogeneic iPSC lines that introduce or correct the E209K pathogenic variant in WT and PACS2 syndrome patient backgrounds. iPSCs are used to differentiate into neural precursor cells (NPCs) and cerebral brain organoids. Through these models, we investigate the impact of PACS2 p.E209K on apoptosis and MAM formation during neurodevelopment. Research outcomes will contribute insights into the pathogenesis of PACS2 syndrome and will be fundamental for the development of treatments and therapies.

Disclosures: C. Bossert: None. **A.D. Guemez-Gamboa:** None.

Poster

PSTR099: Angelman and Other Developmental Disorders

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.12/A12

Topic: A.07. Developmental Disorders

Support: Smart Loire Valley

Title: Multidimensional assessment of spontaneous motor function and voice production in newborn infants

Authors: *J. HEATHCOCK[1], M. LATINUS[2];
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Abstract: Background: Assessment of infant behavioral development is central to identifying children with neurodevelopmental disabilities. With advances in digital monitoring, patient- and parent-collected health care information, and noninvasive video-audio analysis, multidimensional assessments (e.g. motor, voice, parent-reported outcome measures) has the potential to improve detection of neurodevelopmental disabilities. **Objective:** The aim of this study is to test the feasibility and acceptability of collecting video-audio recordings of spontaneous motor and voice behaviors of infants for multidimensional assessment in inpatient and home environments. **Methods**: N=11 infants (36 - 41 weeks gestational age) and their families were enrolled in a longitudinal study to test the feasibility of assessment via experimenter-collected recordings in inpatient settings and via remote parent-collected recordings at home. Questionnaires were used to assess acceptability of participation in a larger trial and to check for barriers and preferences. **Results**: Recruitment, enrollment, and retention rates were sufficient for the current approach and informed future adaptations for a larger scale study. Unknown discharge date was the most common barrier for recruitment. Retention and technology difficulties were the most common barriers for the remote parent-collected session. Inpatient research staff, in person parent training, reminder calls and text messages, and technology assistance were used to enhance engagement and reduce technology barriers at home. Questionnaire responses suggest high levels of acceptability of the assessment (motor, voice, parent-reported outcome measures) including a longer follow up. General movement assessments and acoustic analysis were completed with sufficient variation. **Conclusions**. Assessment of spontaneous motor and voice behaviors in infants is feasible and shows moderate-high levels of acceptability which could generate a new metric for validation and diagnostic prediction in neurodevelopmental disabilities.

Disclosures: J. Heathcock: A. Employment/Salary (full or part-time):; The Ohio State University, iBrain, The University of Tours. 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.; Loire Valley Research Program. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); n/a. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); n/a. E. Ownership

Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); n/a. F. Consulting Fees (e.g., advisory boards); n/a. **M. Latinus:** A. Employment/Salary (full or part-time):; ibrain. 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.; n/a. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); n/a.

Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.13/A13

Topic: A.07. Developmental Disorders

Support: NIH/NINDS R03 NS127256
National MPS Society
NIH/NCATS UL1 TR002345

Title: Classifying genetic variants in Hunter Syndrome using RaftSeq

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Abstract: Mucopolysaccharidosis Type II (MPS II) or Hunter syndrome is a lysosomal storage disorder caused by mutations in the IDS gene, resulting in insufficient production of the iduronate 2-sulfatase enzyme vital for glycosaminoglycan breakdown within lysosomes. There are many variants of unknown significance (VUS) in the IDS gene that cannot be easily classified as pathogenic or benign. To aid in VUS classification, we used RaftSeq, a functional genomics platform that combines high-content imaging with machine learning on microrafts, to define a cellular phenotype of human A549 cells that were wild-type or engineered to express known pathogenic (G224R and 228fsX), or a known benign (V223I) IDS variant. IDS enzyme assay of isogenic cultures of these lines showed very low or no activity for the pathogenic variants, whereas 7 units/mg protein activity was observed for V223I, and 28 units/mg protein activity for wild-type, as expected. Cells were imaged using a fluorescent confocal microscope and intracellular features were extracted from nucleai and lysosomes on a per-cell basis. Combining lysosomal measurements for intensity, puncta morphology, and texture generated a 'pathogenic score' that separated isogenic cultures of the benign from the two pathogenic variants, with 70% of G224R variant cells, 68% of 228fsX variant cells, and 30% of V223I (benign) variant cells scoring as pathogenic-like. The IDS phenotype was then corrected through rescue experiments applying recombinant IDS enzyme. G224R variant cells showed phenotypic rescue to 50% pathogenic-like 144h after IDS treatment. Likewise, 228fsX cells showed a phenotypic rescue to 59% pathogenic-like 144h after IDS treatment. RNAseq experiments will

evaluate transcriptome changes in IDS-treated and untreated variant cell lines. Deep cellular phenotyping and RaftSeq offer a novel means of evaluating the function of patient-specific IDS variants to improve classification and thereby the diagnostic yield of molecular testing for Hunter syndrome.

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Poster

PSTR099: Angelman and Other Developmental Disorders

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Program #/Poster #: PSTR099.14/A14

Topic: A.07. Developmental Disorders

Support: EMBO Scientific Exchange Grant
PRIN PNRR 2022 P202255794
Famiglie GNAO1

Title: Development of human iPSC-based in vitro systems for modelling GNAO1 disease and drug testing

Authors: *M. BENEDETTI[1], R. DE SANTIS[2], T. D'ANDREA[3], V. DE TURRIS[4], S. MARTINELLI[5], S. FUCILE[6], A. BRIVANLOU[2], A. ROSA[7];
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Abstract: GNAO1 encephalopathy is a rare disease caused by pathogenic variants in the *GNAO1* gene, encoding for the Gαo subunit of G-proteins. This protein has a central role in the nervous system regulating both synaptic activity and neurodevelopment. Patients affected by this pathology develop different set of symptoms, including developmental delay, epilepsy and hyperkinetic movement disorder. Currently, effective treatments are still lacking, thus the aim of this study is to create an iPSC-based platform for GNAO1 disease modelling and drug testing, taking advantages of cortical differentiation and micropatterning models. taking advantage of CRISPR-Cas9 system, we created a collection iPSC lines carrying three different pathogenic variants with their respective isogenic controls. Initially, we characterized the p.G203R variant since it is one of the most represented and also the most severe. At early stage of cortical differentiation, we observed altered expression of neural and WNT-related genes and concomitant defects in the formation of neural rosettes. At later time points, p.G203R neurons showed an imbalance between neural progenitors, neurons and astrocytes. Functional analysis

exhibited lower basal intracellular calcium levels, a reduction of spontaneous activity, and a smaller response to several neurotransmitters. Collectively these finding suggest defective differentiation processes leading to significant impairments of functional maturation and neuronal activity. Interestingly, we confirmed the early defects also in the other two pathogenic variants, p.S47G and p.E246K. To the best of our knowledge, how these two mutations affect neurodevelopment has been never explored before. These data highlight that different pathogenic variants share common neurodevelopmental defects, may related to altered WNT signalling. We have then established micropatterning models of gastrulation and neurulations. Gastruloids carrying the p.G203R and the p.E246K showed a strong reduction of ectodermal area, the germ layer precursor of the nervous system, while p.E246K neuruloids exhibited an aberrant neuroectodermal arrangement. Interestingly, we observed that caffeine treatment was able to selectively increase the SOX2+ area in gastruloids carrying GNAO1 pathogenic substitutions but not in the wild-type control. In future, micropatterning systems, which are highly fast, scalable and reproducible models, could be used to preliminary test many different compounds in order to find the best drug candidates to test on cortical neurons

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Poster

PSTR099: Angelman and Other Developmental Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.15/A15

Topic: A.07. Developmental Disorders

Support: NACC1 Sundry Fund

Title: A missense mutation in the gene NACC1 which causes profound developmental delay in humans causes changes in synaptic and adhesion properties in cultured human neuron and neural stem cell models

Authors: *M. DEEHAN[1], E. WEISMAN[1], S. LIU[1], E. SAPP[1], A. NOORI[1], S. DAS[1], M. BRODSKY[2], M. DIFIGLIA[1], K. B. KEGEL[1], M. IULIANO[1], R. ROBERTSON[1]; [1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Molecular, Cell and Cancer Biol., UMass Chan Med. Sch., Worcester, MA

Abstract: In 2017 a *de novo* point mutation (c. 892C>T, p. R298W) in the gene Nucleus Accumbens 1 (*NACC1*) was discovered to cause profound neurodevelopmental delay, microcephaly, severe epilepsy, irritability, failure to thrive, and stereotypic, involuntary movements. NACC1 has previously been characterized as a transcriptional repressor in the brain and overexpressed in various cancers yet its cellular and molecular functions are poorly characterized in brain. Utilizing CRISPR-Cas9 editing, we established isogenic embryonic stem cells (ESC) harboring heterozygote and homozygote R298W mutation and studied differentiated

control and R298W mutant human excitatory cortical neurons. Immunofluorescence revealed that NACC1 is predominantly in the nucleus in human neurons. Western blot analysis showed no change in abundance in mutant NACC1 compared to wildtype protein. RNA sequencing and bioinformatic analysis on NACC1 R298W control and homozygote cortical neurons revealed 4,354 upregulated and 4,360 downregulated differentially expressed genes. Ongoing work is being done to investigate if some of these gene expression changes reflect altered developmental patterning. Reactome pathway analysis showed upregulated genes were significantly enriched to pathways related for synaptic function while downregulated genes enriched for pathways related to extracellular matrix and adhesion. At the protein level, expression of the presynaptic protein SNAP25 and postsynaptic protein Homer 1 were significantly increased, supporting a potential synaptic dysregulation also seen in brain of a mouse model of the disorder we recently reported (Deehan et al., J Neursci. 2024). To determine if the downregulated pathways in human neurons that related to extracellular matrix and adhesion were functionally relevant, we also generated human neural stem cells (NSCs) from our control and homozygote NACC1 R298W ESC cell lines and are subjecting them to adhesion assays using different substrates. Overall, these data reveal that NACC1 R298W homozygous neurons have robust phenotypes that will be useful for identifying pathogenic mechanisms and assessing therapeutic interventions to treat the disorder.

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Poster

PSTR099: Angelman and Other Developmental Disorders

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Program #/Poster #: PSTR099.16/A16

Topic: A.07. Developmental Disorders

Support: Loulou Foundation

Title: Preclinical and Clinical evidence on Alpha-Tubulin Post-translational Modifications as Potential Translational Biomarkers in CDKL5 Deficiency Disorder

Authors: *S. WANINGER[1], A. M. THORNTON[1], C. DE PASQUALE[1], A. M. FREEBURN[1], I. BARBIERO[2], C. KILSTRUP-NIELSEN[2], J. KEALY[1], M. BIANCHI[1];
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Abstract: CDKL5 deficiency disorder (CDD) is an X-linked neurodevelopmental disease caused by mutations in the *CDKL5* gene and characterized by early-onset, refractory epilepsy, and cognitive and motor developmental delays. CDKL5 is a serine-threonine kinase with reported involvement in the regulation of the cytoskeleton and microtubule (MT) network. Loss of CDKL5 results in altered neuronal morphology and defects in phosphorylation and regulation of MT associated proteins (MAPs), including EB2. Neurons possess two compartmentalized pools

of MTs, less and more dynamic, and α-tubulin posttranslational modifications (PTMs) such as acetylation (Acet-Tub), associates with the dynamic status, a process that is vital in neurodevelopment and remodeling of synaptic connections. Tubulin acetylation at Lys40 generates Acet-Tub, a hallmark of less dynamic MTs. Altered microtubule dynamics are associated with the pathogenesis of neurodevelopmental and neuropsychiatric disorders. A comparison of hippocampal and plasma expression of the α-tubulin PTM ratios [Acet-Tub/Total alpha-tubulin (Tot-Tub)] and phospho-EB2 from *CDKL5* mutant mice (exon 6; male, N=32; female, N=34) and wild type (WT; male, N=35; female, N=33) was performed using infrared western blot (IFWB). IFWB was also used to measure Acet-Tub/Tot-Tub from plasma of CDD patients (N=17) and compared with healthy, age-matched controls (N=14) were measured using IFWB. Electrochemiluminescence (ECL; Mesoscale) was used to analyze neurofilament light (NfL), brain derived neurotrophic factor (BDNF) and a panel of cytokines/chemokines. Acet-Tub/Tot-Tub is overexpressed in the hippocampus and plasma of *CDKL5* mutant mice along with downregulated phospo-EB2. Acet-Tub/Tot-Tub is overexpressed in plasma of CDD patients and paralleled by increased NfL, decreased BDNF and IL-10. There is an inverse correlation between plasma Acet-Tub/Tot-Tub overexpression and BDNF downregulation in CDD subjects that is independent from the patients' age. Acet-Tot-Tub overexpression in both *CDKL5* mutant mice and CDD subjects is indicative of dysregulated microtubule dynamics. Assessment of MT dynamics serves as translational biomarkers for CDD and other neurodevelopmental disorders as well as neuropsychiatric disorders. In addition, the MT network represents a promising target for the development of pharmacological interventions that positively affect MAP functioning and α-tubulin PTMs regulation.

Disclosures: S. Waninger: A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **A.M. Thornton:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **C. De Pasquale:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **A.M. Freeburn:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **I. Barbiero:** 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.; University of Insubria. **C. Kilstrup-Nielsen:** 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.; University of Insubria. **J. Kealy:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience. **M. Bianchi:** A. Employment/Salary (full or part-time):; Ulysses Neuroscience.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.01/A17

Topic: A.09. Adolescent Development

Support: DFG – EXC 2050/1 – ID 390696704

Title: Effects of Multisensory Congruence-Based Plausibility on Cortical Activity during Vibrotactile Perception in Virtual Environments in Youth

Authors: *A. PALMISANO[1,2], K. KANG[2,3], K. KARAN[1,2], R. ROSENKRANZ[1,4], M. ALTINSOY[1,4], S.-C. LI[1,2];
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Abstract: The plausibility of multisensory events in virtual reality (VR) represents a challenge for constructing realistic virtual experiences. Implications span from therapeutic to educational and entertainment purposes. However, our understanding of the effects of perceptual plausibility on brain processes in multisensory virtual environments is limited, particularly concerning the age range between childhood and adulthood. Peri-adolescents and adolescents are among the primary users of VR. To fill this gap, we assessed how multisensory plausibility (i.e., operationally defined as multisensory congruence between audio-visual contextual information and vibrotactile stimulations) in VR-based vehicle riding scenarios may modulate cortical activity in 11- to 17-year-olds (N = 60, 30 males). An event-related study design was used to measure brain hemodynamic responses in frontal and sensorimotor regions using functional Near-Infrared Spectroscopy (fNIRS) while participants were exposed to various scenarios simulating the “passenger’s experience” (i.e., audio-visual scenes with roads of different surface roughness combined with vibrotactile stimulations of different intensities). Previous evidence in young adults reveals that weaker but plausible stimulation can lead to greater brain responses than stronger but implausible ones. Given the gradual development of the sensory and motor association cortices and the late maturation of the frontal lobe, we expected brain responses during this life period to be less sensitive to multisensory plausibility than in adulthood. Preliminary results from linear mixed-effects models in about 40 participants show a significant main effect of vibrotactile intensity on concentration levels of oxygenated haemoglobin (HbO) in sensorimotor (F (1, 1831) = 19.45, $p < .0001$) and prefrontal (F (1, 1894) = 11.86, $p = .0006$) regions, with low-intensity stimulations eliciting higher brain responses. Interestingly, significant plausibility (F (1, 6404) = 10.05, $p = 0.0015$) and scene*plausibility (F (3, 6404) = 12.78, $p < .0001$) effects also emerged, with scenarios of low plausibility eliciting greater responses, specifically in scenes (cobblestone roads) where stronger vibrotactile feedback is expected. These findings diverge from the activation patterns observed in adults and reflect age-related differences in the integration of sensory information and experience-based expectations. Furthermore, our results suggest that age-related differences in brain responses to cross-modal stimulations should be considered in the design of ecologically valid and age-inclusive VR environments.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.02/A18

Topic: A.09. Adolescent Development

Title: Reduced Integrity of White-Matter Tracts in Adolescents with ADHD: A Symptom Specific Investigation

Authors: *R. BHAGAR[1], K. LUKING[2];
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is an executive function disorder characterized by deficits in attention, hyperactivity, and impulsivity. ADHD is prominent among children and may cause cognitive and behavioral effects. The pathophysiology of ADHD in adolescents remains unclear due to its heterogeneous symptoms and atypical development. We aim to uncover structural connectivity deficits in adolescents. We utilized the Adolescent Brain Cognitive Development (ABCD) study to examine white matter tracts in adolescents. ADHD was assessed using caregiver report on the Child Behavior Checklist (CBCL). Demographics and internalizing symptoms were also reported by caregiver, while impulsivity and motivation were self-reported. Cross-sectional analyses were run at baseline (mean age = 9.9) on test and re-test cohorts. Participants were followed for 2 years for longitudinal analyses. 27 white-matter tracts from previous literature were analyzed in a cross-sectional linear mixed-effects model (LMM) resulting in 5 Bonferroni significant tracts in test & re-test cohorts. The symptom-specificity of those 5 were analyzed at baseline and showed the strongest relationship with inattention. A subsequent longitudinal LMM was ran to investigate if changes in ADHD symptoms correspond with changes in structural connectivity. Only 1 tract was nominally significant in the test cohort and did not replicate. However, baseline ADHD symptoms failed to predict longitudinal in structural connectivity, and did not show any sex-specific effects. Here we show a relationship between ADHD symptom severity and structural connectivity in adolescents that can be broken down by symptom. Furthermore, we provide limited evidence for unique developmental trajectories in ADHD, calling for more longitudinal studies.

Disclosures: R. Bhagar: None. **K. Luking:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

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Topic: A.09. Adolescent Development

Support: NIH Grant AA028840

Title: Heterogeneous brain functional mapping of childhood psychiatric symptoms

Authors: *L. MILECKI[1], A. KUCEYESKI[1,2], M. R. SABUNCU[1,2,3], Q. ZHAO[1];
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Abstract: Adolescence is characterized by the profound and heterogeneous remodeling of neural circuits and is a sensitive period when psychiatric symptoms first emerge. Learning the association between psychiatric phenotypes and resting-state functional MRI (rs-fMRI) data can improve the understanding of brain-symptom mapping and, thus, direct prevention. Still unknown, however, is whether the mapping is homogeneous in the population or varies with demographic and environmental factors. In this study, we extracted relevant relationships between rs-fMRI and the 8 symptom scores of the Child Behavior Checklist (CBCL) at the baseline visit of 9544 adolescents (9-10 years old, 4792 boys/4752 girls) from the Adolescent Brain Cognitive Development (ABCD) study. Canonical Correlation Analysis (CCA) was used to learn the mapping from CBCL scores to cortical-to-cortical (CC) and cortical-to-subcortical (CS) functional connectivity separately. Both rs-fMRI features and CBCL scores underwent linear residualization for confounding adjustment with age, sex, race, and parental education. The model was evaluated on 10 random train/test sets in a leave-three-sites-out fashion, with a 50-fold inner cross-validation on the train set to tune the ridge coefficients of the regularized CCA. This procedure was repeated in sub-populations, including in each sex and adolescents with low and high adverse childhood experiences (ACE, threshold defined as the median of CDC-Kaiser ACE scores). Experiments revealed 2 reproducible components in CBCL-CC mapping ($r=0.14, 0.11$, $p<0.001$ z-test) and 2 components in CBCL-CS mapping ($r=0.15, 0.11$). These correlations were driven by the mapping from the dorsal attention and cingulo-opercular networks to rule-breaking behaviors and from the sensorimotor network to attention scores. The sub-population analysis revealed that the correlation strength of CBCL-CC components was significantly higher in girls than in boys ($t_{18}=0.36$, $p=0.002$). This difference was driven by sex-specific mapping, with girls having greater loadings on attention and thought problems and boys having greater loadings on rule-breaking and aggressive behaviors ($p<0.001$, permutation test). Although ACE-related components manifested no difference in the correlation strength, the mapping in the low-ACE group was driven by higher attention, thought, and depressive symptoms ($p<0.001$). These results on establishing neuromarkers linked to adolescent psychiatric symptoms and cohort-specific brain-behavior mappings set the path for future research to unveil heterogeneous neurobiological targets for personalized treatment design and early risk assessment.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Topic: A.09. Adolescent Development

Support: NIH Grant HD108757

Title: Neural Mechanisms of Adolescent Sustained Attention

Authors: *A. BOLARAM[1], D. K. GREY[2], C. ORIHUELA[3], S. MRUG[3], D. C. KNIGHT[3]; [1]The Univ. of Alabama at Birmingham, Birmingham, AL; [2]Psychology, The Univ. of Alabama at Birmingham, Birmingham, AL; [3]Psychology, Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Attention is a fundamental process that modulates the performance of daily activities. Attention supports the identification of task-relevant information and rejection of task-irrelevant information to effectively execute goal-directed behaviors. Sustaining attention is important for goal-oriented behaviors (e.g., reading, listening to lecture, completing homework). Brain maturation during adolescence may be important for the ongoing development of sustained attention processes. However, investigations of the efficiency of sustained attention processes during adolescence are relatively scarce. Therefore, neuroimaging research into individual differences in sustained attention in adolescence may provide a better understanding of neurodevelopmental processes that underlie attention. The current study was designed to identify adolescent brain activity that underlies sustained attention and varies with performance during a sustained attention task. Forty participants [20 female, age = 15 ± 0.80 years (Mean ± SD)] completed the paced visual serial addition test (PVSAT) during functional magnetic resonance imaging (fMRI). Participants viewed single digit numbers (3 s duration) on a screen during sustained attention and control conditions of the PVSAT. Participants either reported the sum of the two most recent numbers (i.e., sustained attention) or reported the number on the screen without adding (i.e., control). The task was presented during two fMRI scans that contained 4 blocks of control trials that alternated with 3 blocks of sustained attention trials (10 trials/block; 1 s inter-trial interval). Task instructions were presented (6 s duration) prior to each block of trials. The percentage of correct responses across sustained attention vs control conditions served as a measure of performance accuracy. Neuroimaging data were acquired on a 3T Siemens Prisma scanner. Data were analyzed with a linear mixed effects model with performance accuracy as a covariate. Results revealed a main effect of PVSAT (i.e., sustained attention vs control). Greater dorsolateral prefrontal cortex (PFC), cingulate gyrus, anterior insula, and inferior parietal lobule activity was observed during the sustained attention than control condition. Results also revealed a significant interaction between PVSAT and performance accuracy. Performance accuracy during the PVSAT was related to activity within the superior parietal lobe and subcallosal gyrus. These findings suggest that superior parietal lobe and subcallosal gyrus activity may underlie individual differences in sustained attention during adolescence.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Program #/Poster #: PSTR100.05/A21

Topic: A.09. Adolescent Development

Support: MH096889

Title: Effects of early life adversity on functional connectivity of the paraventricular nucleus of the thalamus during adolescence

Authors: *B. LEONARD[1], J. RASMUSSEN[1], S. L. SMALL[2], C. SANDMAN[1], H. STERN[1], T. Z. BARAM[3], L. GLYNN[4], E. DAVIS[5], M. A. YASSA[6];
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Abstract: Rationale: Emotional and memory circuit maturation is shaped by sensory signals in the environment during early life. There is growing evidence that the paraventricular nucleus of the thalamus (PVT) acts as a central hub that is involved in storing memories of early life adversity. However, PVT functional connectivity has not yet been evaluated in the adolescent human brain, and the impact of early life adversity (ELA) on the development of PVT connectivity to emotional and memory circuitry is largely unknown. **Methods:** We used two cohorts of this study. The first is drawn from the Conte Center @ UCI study, a longitudinally monitored cohort of mother-child dyads (n = 152, children are 78 female, 74 male, range 9-17 years). Unpredictability of early life environment was quantified in this cohort using the Questionnaire of Unpredictability in Childhood (QUIC) and three fMRI imaging sessions were acquired during childhood and early adolescence. As a first step towards validation, a sub-sample consisting of baseline visits from the two largest sites within ABCD was analyzed (n = 674, children are 347 female, 307 male, range 8.9-11 years) and chosen as a validation cohort. Image quality, site and nesting in family structure were controlled for in ABCD analysis. Early life adversity in ABCD was quantified using Adverse Childhood Experiences (ACEs). Seven bilateral regions of interest were selected a priori based on preclinical literature. Measures of functional connectivity (FC) between these regions and the PVT were considered in seven independent mixed effects models testing for a main effect of ELA adjusted for age at scan and sex. **Results:** Preliminary findings suggest that ELA is associated with reduced PVT-amygdala FC in both Conte Center ($T = -2.9$, $p = 0.004$) and ABCD ($T = -2.3$; $p = 0.02$) cohorts. We also found that PVT-hippocampus FC was negatively associated with ELA measures in females across both cohorts (Conte Center QUIC: $T = -2.37$, $p = 0.02$, Conte Center ACEs: $T = -1.91$; $p = 0.06$; ABCD ACEs: $T = -2.82$, $p = 0.005$). **Discussion:** Two measures of ELA (unpredictability of early environment and adverse childhood experiences), across two cohorts, are associated with reduced FC of the PVT to emotional memory networks (amygdala and hippocampus). Early life adversity has been shown to induce synaptic pruning in the hippocampus and impact the structure and function of the PVT circuitry in animal models. These data in humans are consistent with data from animal models and suggest that PVT and its connectivity with emotional memory circuitry may be a key hub of vulnerability in the adolescent brain and requires further investigation.

Disclosures: B. Leonard: None. **J. Rasmussen:** None. **S.L. Small:** None. **C. Sandman:** None. **H. Stern:** None. **T.Z. Baram:** None. **L. Glynn:** None. **E. Davis:** None. **M.A. Yassa:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.06/A22

Topic: A.09. Adolescent Development

Support: NIH Grant MH080243
Staunton Farm Foundation
Brain and Behavior Research Foundation

Title: Characterizing the role of striatal dopamine-related neurophysiology in substance use trajectories and response inhibition in youth at risk for problematic substance use

Authors: *A. C. PARR[1], A. OJHA[2], F. J. CALABRO[3], W. FORAN[4], D. FITZGERALD[1], S. F. TAPERT[5], K. NOONER[6], W. THOMPSON[7], D. GOLDSTON[8], M. D. DEBELLIS[9], D. CLARK[1], B. LUNA[4];
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Abstract: Little is known about dopamine (DA) development and substance use risk in adolescence. Differences in response inhibition and striatal reward sensitivity have been shown in adolescents with increased substance use vulnerability (Tervo-Clemmens et al., 2017,2020). We have recently shown that striatal tissue iron, reflecting DA availability (Larsen et al., 2020), contributes to frontostriatal development (Parr et al., 2021) and response inhibition (Parr et al., 2022) in normative adolescence. Here, we characterize the role of striatal neurophysiology in substance use trajectories and response inhibition across adolescence.
The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) study combines neuroimaging with assessments of cognition and substance use in a large, multisite, longitudinal cohort of adolescents and young adults (N=831, 5 sites, 423F, baseline age=12-22yo, 1-9 visits, N sessions=6268). MR-based indices of striatal tissue iron were obtained via time averaged and normalized T2*-weighted images (nT2*w; Peterson et al., 2019). Response inhibition was assessed using the anti-saccade task (Duke & Pittsburgh sites; N=276, 150F, 1-5 visits, N sessions=682). General additive mixed models examined non-linear trajectories across measures, and associations between substance use, nT2*w, and response inhibition. Substance use trajectories were characterized using Growth Mixture Models.
In confirmation of prior studies (Peterson et al., 2018), nT2*w indices of striatal DA-related

neurophysiology increased (F=291.60, p<.001) and anti-saccade performance improved (F=31.10, p<.001) across adolescence. *Low* nT2*w was associated with higher levels of substance use (x^2=7.09, p=.03) and poorer inhibitory control (x^2=7.36, p=.03) relative to *high*. Growth Mixture Models revealed 3 substance use trajectories: *low* (low use across development; 24% of participants), *youth peak* (peak use in adolescence/youth followed by decreases into adulthood; 47% of participants), and *escalating* (linear increases in use from adolescence into adulthood; 29% of participants). Youth peak trajectories were particularly associated with *low* nT2*w and *low* anti-saccade performance.
We provide novel *in vivo* evidence that individual differences in DA-related neurophysiology contribute to substance use, potentially by modulating response inhibition, and may be particularly implicated in adolescent/young adult substance use. Specifically, *lower* striatal iron, reflecting low DA availability, was predictive of increased substance use risk, which may reflect higher risk-taking behavior and decreases in response inhibition.

Disclosures: A.C. Parr: None. **A. Ojha:** None. **F.J. Calabro:** None. **W. Foran:** None. **D. FitzGerald:** None. **S.F. Tapert:** None. **K. Nooner:** None. **W. Thompson:** None. **D. Goldston:** None. **M.D. Debellis:** None. **B. Luna:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.07/A23

Topic: A.09. Adolescent Development

Support: NIMH R00 MH125021

Title: Brain criticality emerges with developmental shifts in excitation-inhibition balance, setting the stage for cognitive control in adulthood

Authors: *A. WESTBROOK[1], F. J. CALABRO[2], A.-E. AVRAMIEA[5], K. LINKENKAER-HANSEN[6], S. MCKEON[3], B. LUNA[4];
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Abstract: Adult brains, at rest, operate near criticality - at the boundary between super-critical, excitation-dominant regimes, and sub-critical, inhibition-dominant regimes, with radically divergent dynamics on either side. Dynamics which emerge right at criticality confer susceptibility, entropy, and information transmission, with profound implications for cognitive control. Enhanced information transmission, for example, should strengthen top-down control over sensorimotor regions, while greater susceptibility should bias flexibility over stability. Here, we study dynamical properties of rest EEG recordings during N = 310 sessions from 169 healthy

participants from 10 to 33 years old. Our analyses reveal that brains operate closer to criticality as they mature, as indexed by stronger long-range temporal correlations and higher bistability in band-limited amplitude. Moreover, relationships between amplitude and variability indicate a developmental shift towards decreasing excitatory versus inhibitory neurotransmission with age. Finally, as predicted, people whose brains operate closer to criticality show less stability during a memory-guided saccade task with more trial-wise variability in accuracy and reaction times, controlling for age. Also, higher excitation-inhibition ratios correspond with better top-down control in terms of higher anti-saccade accuracy. We conclude that developmental shifts in excitation-inhibition balance towards criticality set the stage for cognitive control in adulthood.

Disclosures: A. Westbrook: None. **F.J. Calabro:** None. **A. Avramiea:** None. **K. Linkenkaer-Hansen:** None. **S. McKeon:** None. **B. Luna:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.08/A24

Topic: A.09. Adolescent Development

Support: Ann S. Bowers Foundation for the Ann S. Bowers Women's Brain Health Initiative

Title: Sex differences in brain maturation during puberty: a study of control energy and dopaminergic influence

Authors: *P. YANG[1], L. SCHILLING[2], K. JAMISON[3], A. KUCEYESKI[4];
[1]Cornell Univ., ITHACA, NY; [2]Weill Cornell Med., Brooklyn, NY; [3]Weill Cornell Med., New York, NY; [4]Radiology, Weill Cornell Med. Col., New York, NY

Abstract: The human brain undergoes critical changes along the stages of puberty, which are characterized by the interaction of hormonal and neurodevelopmental changes. We utilize resting-state functional magnetic resonance imaging (rs-fMRI) regional time-series and structural connectome (via deterministic tractography) MRI data of 608 subjects (8~22 years old) from the Human Connectome Project for Development (HCP-D) to evaluate sex differences between pre- and post-pubertal stages. Following a network control theory approach, we quantify at a regional level the effort required to transition from one brain state to another, or control energy. We hypothesize that brain regions exhibiting marked sex differences in control energy after puberty compared to before puberty would be dopamine-receptor enriched, possibly due to the modulatory effects of estradiol on the dopaminergic system. In an analysis of covariance (ANCOVA) including sex, age, puberty status (i.e., before/after), sex*puberty status, sex*age, and in-scanner motion (i.e., mean framewise displacement), we find pronounced sex differences in the left medial orbitofrontal cortex (F-stat = 12.4241, pFDR = 0.0384), and sex*age differences in the right superior parietal grey matter(F-stat = 10.8482, pFDR = 0.0442) and the

right cerebellar cortex(F-stat = 14.0638, pFDR = 0.0162). We also find significant correlations between the regional effect of sex*age and D1 receptor densities (Spearman rho = -0.2999, p = 0.0116), and sex*puberty and D2 receptor densities (Spearman rho = -0.2561, p = 0.0172), while there is only one a significant correlation between the regional effect of sex and D2 receptor densities within cortex and cerebellum regions (Spearman rho = -0.2999, p = 0.0116) presented when including excluding the subcortex. These findings underscore a nuanced relationship between sex, puberty, age, and dopaminergic signaling such that regions with less dopaminergic D1/D2 receptors have larger effects of sex on control energy. The present study provides a deeper understanding of the neurobiological substrates underlying sex-specific brain maturation and stands to contribute to the broader comprehension of how hormonal changes during puberty might selectively influence neural dynamics, potentially shaping behavior and cognitive outcomes in a sex-dependent manner.

Disclosures: P. Yang: None. **L. Schilling:** None. **K. Jamison:** None. **A. Kuceyeski:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Program #/Poster #: PSTR100.09/A25

Topic: A.09. Adolescent Development

Support: R01EB022573
U24NS130411
R01AG066650
R01MH120811

Title: Discovering fine-grained functional connectivity patterns predictive of neurocognition in youth with optimized predictive modeling

Authors: H. LI, ***Y. FAN**;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Functional MRI studies have discovered functional connectivity (FC) patterns associated with behavior traits using either whole-brain or region-wise predictive modeling techniques. However, the whole-brain modeling techniques lack interpretability and the region-wise modeling tools often have limited predictive accuracy. To overcome these limitations, we develop an interpretable end-to-end predictive modeling method to simultaneously learn fine-grained FC patterns that are predictive of behavior traits, both individually and collectively, at a participant-level for capturing the overall association of FC patterns with a target trait under investigation. Particularly, we build a predictive model to learn a relevance score with a specific prediction head for each brain region with its whole-brain FC measures as features and integrate the region-wise prediction results to obtain the participant-level prediction. The model is optimized by minimizing differences between the predicted and measured traits at both region-

level and participant-level on a training dataset. We have validated the proposed method using FC data of 6798 participants from the Adolescent Brain and Cognitive Development (ABCD) study for predicting neurocognition in three domains, including General Cognition, Executive Function, and Learning/Memory. Experimental results have demonstrated that brain regions within ventral attention network, frontal parietal network, and cingulo-opercular network were collectively associated with these neurocognitive traits and the predicted cognitive traits were significantly correlated with the measured traits on held-out testing subjects (five-fold-cross validation, General Cognition: r=0.51; Executive Function: r=0.24; Learning/Memory: r=0.31). The predictive accuracy was significantly higher than those obtained by alternative whole-brain FC based prediction model and ensembles of region-wise models, indicating that our method can effectively characterize fine-grained FC patterns associated with neurocognition in youth, both individually and collectively.

Disclosures: H. Li: None. **Y. Fan:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.10/A26

Topic: A.09. Adolescent Development

Title: The effect of community cohesion on working memory as moderated by right fusiform gyrus activity during the emotional n-back task

Authors: J. ALTMAN, M. GRAF, E. ROBERTSON, ***N. WOON**, C. MIKKELSEN; Neurosci. Dept., Smith Col., Northampton, MA

Abstract: Prior research has established that high levels of community cohesion are associated with improved cognitive functioning and fewer depressive symptoms (Zhou et al., 2022). However, there are a limited number of studies looking into the effects of community cohesion on specific cognitive functions, such as working memory. Here, we utilized neural data and surveys from the Adolescent Brain Cognitive Development (ABCD) study to explore the relationship between neighborhood dynamics, working memory, and neural activity in 11-12 year olds. Specifically, we used the measures of performance on the emotional n-back task, neural activity for 2-back trials as compared to 0-back trials within a high memory load task in the right fusiform gyrus during the emotional n-back task and parental surveys. We hypothesized that activity in the right fusiform gyrus will be positively correlated with working memory, as measured by the number of correct responses for both high and low memory load conditions on the emotional n-back task. We also hypothesized that children who have lived in more communally cohesive neighborhoods will exhibit better working memory than children who lived communally incohesive neighborhoods. Finally, we hypothesized that the relationship between community cohesion and working memory is moderated by brain activation in the right fusiform gyrus during the emotional n-back task. We found that activity in the right fusiform

gyrus was significantly correlated with performance on the emotional n-back task (p= 0.0124). Additionally, we observed that neighborhood cohesion and the performance on the emotional n-back task were not significantly correlated (p= 0.268). This study reveals new insights into how cognitive impacts of childhood neighborhoods can have longitudinal effects on working memory. Future work can continue to look into the potential for differential influences of the community environment on working memory.

Disclosures: J. Altman: None. **M. Graf:** None. **E. Robertson:** None. **N. Woon:** None. **C. Mikkelsen:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.11/A27

Topic: A.09. Adolescent Development

Support: National Institute of Child Health & Human Development R21 HD108757 (Mrug & Knight)

Title: Adolescent neural reactivity to stress varies with dietary nutrients

Authors: *D. K. GREY[1], A. BOLARAM[1], C. A. ORIHUELA[1], R. EVANS[2], S. MRUG[1], D. C. KNIGHT[1];
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Abstract: The nutrients people consume in their diet are important factors that underlie healthy emotional function. The role diet plays in emotional functioning is particularly important to study in adolescence, when substantial neural and emotional development occurs. For example, diet may affect emotional function through its role in stress reactivity (e.g., hypothalamic-pituitary-adrenal (HPA) axis). For example, deficient levels of magnesium, zinc, and iron are associated with greater stress via HPA axis dysregulation, while vitamin B6 and B12 supplementation are associated with reduced stress. Stress reactivity, and related emotional processes, are mediated by a neural network that includes the prefrontal cortex (PFC), inferior parietal lobule (IPL), hippocampus, and amygdala. However, the relationships between specific nutrients and stress-elicited activity within these brain regions are unclear. Therefore, this project investigated the relationship between adolescent dietary nutrient intake and stress-elicited brain activity. We hypothesized that greater intake of magnesium, zinc, iron, and vitamins B6 and B12 would be negatively associated with stress reactivity in brain regions that support emotional function (e.g., PFC, IPL, hippocampus, amygdala). Neural reactivity to stress was assessed in 35 adolescents using the Montreal Imaging Stress Task during functional magnetic resonance imaging. Adolescent diet was measured using a 24-hour dietary recall, and the intake of specific nutrients was calculated using Nutritionist Pro. Linear mixed-effects models predicted stress-

elicited brain activity from dietary nutrient intake (i.e., magnesium, zinc, iron, vitamins B6 and B12). Covariates included race, sex, and socioeconomic status. Dietary zinc, iron, and vitamin B6 and B12 intake was negatively associated with stress-elicited dorsolateral PFC, dorsomedial PFC, and hippocampal activity. Zinc was also positively associated with IPL activity. Similarly, dietary magnesium levels were positively associated with dorsolateral PFC activity. The present results suggest that dietary nutrient intake may alter the neural response to stress within brain regions that support emotional function (e.g., PFC, IPL, hippocampus). These findings may have important implications for understanding the interrelationships among adolescent diet, neural function, and emotional processes.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.12/A28

Topic: A.09. Adolescent Development

Title: Verbal Ability and Functional Network Organization in Early Adolescence

Authors: *E. M. KOITHAN, D. V. DEMETER, S. ALI, M. FEIGELIS, A. BAIM, S. ZREIK, D. J. GREENE;
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Abstract: Verbal ability - the capacity to understand, interpret, and generate language effectively - is central to human interaction with wide-ranging impacts. Differences in cognition, including verbal ability, may be reflected in individual differences in the functional organization of the brain. Dense sampling of fMRI data from individual people using precision functional mapping (PFM) is required to reliably characterize regions of high inter-individual variability, while thousands of individuals are needed to reliably associate brain function to behavior. This project combines these approaches to determine if regions of high inter-individual variability in brain functional connectivity relate to individual differences in verbal ability in a sample of 11-13 year olds from the Adolescent Brain Cognitive Development (ABCD) Study (n = 2713, M_{Age} = 12.01 years, SD_{Age} = 0.65 years). For each adolescent, we computed the Fisher z-transformed correlation between the resting-state fMRI timecourses of 15 regions of high inter-individual variability (defined from PFM data; n = 12, ages 8-12) and the mean timecourse of 14 large-scale functional brain networks (defined using an ABCD group average). Our findings reveal that functional connectivity between a region of the posterior cingulate cortex and the retrosplenial temporal network positively predicts receptive vocabulary ability after controlling for age, sex, race, and socioeconomic status. This relationship remained significant in mixed-effects linear regression models controlling for age, sex, handedness, components of genetic ancestry, study site, income-to-needs ratio, and the ability to speak multiple languages (with family as a random

effect). Additionally, functional connectivity between regions of the left and right posterior middle temporal gyrus (often active during language processing) and the default mode network positively predicts receptive vocabulary ability, while functional connectivity to the cingulo-opercular action mode network and dorsal attention network negatively predicts receptive vocabulary ability after controlling for age. These results suggest that the deactivation of networks involved in action planning and top-down attention during language processing may facilitate receptive vocabulary ability. These findings deepen our understanding of the neural mechanisms underlying verbal ability and may guide the development of tailored, biologically-based interventions to enhance language skills.

Disclosures: E.M. Koithan: None. **D.V. Demeter:** None. **S. Ali:** None. **M. Feigelis:** None. **A. Baim:** None. **S. Zreik:** None. **D.J. Greene:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.13/A29

Topic: A.09. Adolescent Development

Support: NIA Grant R01 AG064247-04

Title: Hippocampal subfield volumes and physical activity in periadolescent children: preliminary findings from the PRANK-Fit study

Authors: *A. HELLER-WIGHT, A. WILHELM, J. SEXTON, M. K. RAMIREZ, C. J. PHIPPS, D. E. WARREN;
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Abstract: The hippocampus, a structure necessary for normal memory function, exhibits age-related volumetric differences. Specifically, hippocampal development is protracted and regionally heterogenous, making investigation of hippocampal subfield volume changes important for understanding the development of the hippocampus. Additionally, other factors have also been associated with differences in hippocampal volume, whole and subfields, including lifestyle factors such as physical activity (PA). Evidence suggests that PA is associated with total hippocampal volume and subfield volumes in adults, but there has been less attention on how PA may influence the development of hippocampal subfields, specifically during periadolescence, a period of significant brain maturation. Therefore, the current study aimed to investigate the relationship between hippocampal subfield volume and PA measured by accelerometry in a group of healthy periadolescent children aged 8 - 13 years. Cognitive and brain data were collected as part of the NIA-funded Polygenic Risk for Alzheimer's disease in Nebraska Kids (PRANK) Study (R01 AG064247). A subset of PRANK enrollees also participated in the PRANK-Fit sub-study: 46 participants wore an ActiGraph^{TM} accelerometer in order to measure daily, habitual levels of PA, and underwent a 3T MRI study that included a

high-resolution, in-plane, turbo spin echo T2w image of the medial temporal lobe. Automatic Segmentation of Hippocampal Subfields (ASHS) software toolbox was utilized to segment the hippocampus into subiculum, CA1, CA2/3, and dentate gyrus (DG). Raw subfield volumes were correlated with measures of sedentary, moderate, and vigorous PA levels calculated from triaxial acceleration measured with accelerometry. Analysis revealed that total bilateral subiculum subfield volume was significantly correlated with more sedentary behaviors, $r(46) = -.34$, $p < .05$, while the CA1, CA2/3, and DG subfield volumes were not significantly correlated with actigraphy measures in this sample. Characterizing the relationship between hippocampal subfield volumetric differences and lifestyle factors that may be influencing them, including PA, may lead to insights on healthy brain development and function across the lifespan in both health and disease.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Program #/Poster #: PSTR100.14/A30

Topic: A.09. Adolescent Development

Support: University of Arkansas Vice Chancellor for Research and Innovation
Arkansas Biosciences Institute

Title: Reward activity in Nucleus Accumbens (NAcc) correlates with future positive affect

Authors: *G. ALVIDRES[1], E. H. ELLIS[2], J. K. LEONG[2];
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Abstract: What is the neural basis of personality traits such as extraversion? An approach based on the affective circumplex attempts to link activity in target brain areas to high arousal positive emotions, then to the approach behaviors characteristic of trait extraversion. Previous research found that activity in the Nucleus Accumbens (NAcc) during reward anticipation was associated with greater self-report positive affect. However, the neural and trait measures were collected at the same timepoint, therefore could not highlight whether the development of neural circuits precedes stable traits. In this study, we attempted to test whether NAcc activity might precede self-report positive affect. We analyzed data from the Adolescent Brain Cognitive Developmental (ABCD) study when participants were aged 9-11 years old. The neural measures were collected at the baseline timepoint and the self-report positive affect measures were collected 1-year later (n=934). Brain activity was measured with Functional Magnetic Resonance Imaging (FMRI) during the Monetary Incentive Delay (MID) task. We obtained raw percent signal change from the NAcc, which was defined as an 8-mm diameter spheres (centered at Talairach coordinates: +/- 10, 12, -1), and was registered from template-to-native space by

aligning them with each participant's T1 anatomical scan using Advanced Normalization Tools (ANTs). We focused analyses on raw NAcc activity during anticipation and receipt of large gains (+$5). Positive affect 1-year later was measured using the NIH Toolbox Positive Affect Survey (PAS). Results show that NAcc activity in the right hemisphere during reward receipt was associated with higher positive affect 1-year later ($B = 0.08$, $p < 0.05$), with a similar trend in the left hemisphere ($B = 0.06$, $p = 0.09$). Right NAcc activity during gain anticipation was also marginally associated with higher positive affect 1-year later ($B = 0.07$, $p = 0.05$). These results replicate and extend previous findings, and invite future research about the temporal unfolding of brain and trait development.

Disclosures: G. Alvidres: None. **E.H. Ellis:** None. **J.K. Leong:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Program #/Poster #: PSTR100.15/A31

Topic: A.09. Adolescent Development

Support: Marie Sklodowska-Curie Actions: grant agreement No 956414.

Title: Cerebellum gray matter volume across developmental stages and in relation to fear acquisition

Authors: *P. GIL-PATERNA[1], J. MOTILLA HOPPE[2], J. VEGELIUS[3], A. FRICK[4];
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Abstract: The brain changes with development, but developmental changes in cerebellar morphology are not well characterized. Age-related changes in fear conditioning have been reported and suggested to be related to brain maturation, but their relation to potential changes in cerebellar gray matter volume (GMV) remains largely unknown. Here we explore if cerebellum GMV differs across developmental stages and is associated with skin conductance responses (SCRs) during fear acquisition. A cross-sectional healthy sample (N=125) composed of children (n=38; 58% females; mean age=8.1(0.9)), adolescents (n=39; 51% females; mean age=13.7(1.2)), and adults (n=48; 48% females; mean age=34.6(3.1)), underwent a Pavlovian differential cue fear conditioning paradigm and 3T structural magnetic resonance imaging. During fear acquisition, SCRs were collected for one conditioned stimulus (CS+) that was paired with an electric shock on 16 of 20 trials and for one CS (CS-) never paired with an electric shock. The differential SCR (CS+ minus CS-) was used as an index of fear acquisition. The ACAPULCO pipeline (Kerestes et al., 2022) with the SUIT template (Diedrichsen, 2006) was used for cerebellar automatic segmentation into 28 anatomical regions, enabling region-based analyses and voxel-based morphometry. All analyses were corrected for estimated total

intracranial volume and sex. Our preliminary region-based results indicate significant differences in cerebellar GMV between age groups. Specifically, cerebellar GMV in right crus I, was higher in adolescents compared to adults (p_{tukey}=.021; d=0.60). Adolescents also exhibited greater GMV in left (p_{tukey}<.001; d=1.06) and right lobule VIIIa (p_{tukey}=.04; d=0.61) compared to children. SCRs (CS+ minus CS-) during fear acquisition were associated with GMV of left (r=.23; p=.02) and right VIIIa (r=.22; p=.02). This study reveals notable cerebellar morphological variations among developmental stages, suggesting a prominent role of the cerebellum during development and brain maturation. Particularly, the prevalent pattern of results suggest a temporary increase in cerebellar GMV in adolescence. Regarding the positive correlation between fear acquisition and bilateral cerebellar lobule VIIIa, we hypothesize that lobule VIIIa might potentially be involved in the cognitive processing of fear, as previous research has suggested the relevance of that subregion in cognitive functions.

Disclosures: P. Gil-Paterna: None. **J. Motilla Hoppe:** None. **J. Vegelius:** None. **A. Frick:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

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Program #/Poster #: PSTR100.16/A32

Topic: A.09. Adolescent Development

Support: NIH R01 MH067924

Title: Developmental changes in local prefrontal circuitry supports maturation of working memory

Authors: *F. J. CALABRO[1], D. LECROY[2], W. FORAN[3], B. LUNA[4];
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Abstract: Adolescence is a period of significant maturation of cognitive control, supported by the refinement of prefrontal circuitry through synaptic pruning and changes in excitatory-inhibitory balance. However, the effect of these changes on functional signaling properties, including local circuit dynamics, remains only partially characterized. Here, we used data from a longitudinal, adolescent cohort (n=162 individuals ages 10-30, scanned up to three times each at 18mo intervals, n=244 total sessions) with MRI and fMRI data acquired at 7 Tesla. We used resting state fMRI data to compute regional homogeneity (ReHo), a measure of the local functional connectivity, i.e., between a voxel and its immediate neighbors, across the brain. We identified widespread decreases in ReHo with age (p=0.008), including in prefrontal cortex and subcortical regions including the caudate nucleus. These data suggest increasing heterogeneity of functional properties, consistent with increased specialization of functional circuits through

adolescence. Whole-brain ReHo values were significantly associated with developmental improvements in accuracy on a spatial working memory task after controlling for age (p=0.028). Voxel-wise analyses identified this association was driven by regions of inferior prefrontal cortex, insula, and prominently, caudate nucleus, which consistently showed correlations with working memory performance, such that improved accuracy was associated with reduced ReHo. These results suggest remodeling of prefrontal circuitry through adolescence in which increased functional specialization of local circuits supports the maturation of adult-like executive functioning.

Disclosures: F.J. Calabro: None. **D. LeCroy:** None. **W. Foran:** None. **B. Luna:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.17/A33

Topic: A.09. Adolescent Development

Title: Associating impulsivity with the risk of mental disorders and substance use in preadolescents

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Abstract: Series of neurodevelopmental changes occur during adolescence and can lead to an increase of impulsive behaviors in youth. Impulsivity, a key feature for several psychiatric disorders, can be conceptually divided into three main forms: trait, response, and choice impulsivity. Multiple forms of impulsivity may be differentially elevated within specific diagnostic groups. An increase in impulsivity may influence one's initiation and intention of drug use, and adolescents' substance use is a known risk factor for developing neuropsychiatric disorders in adulthood. Despite collaborative efforts to educate youth on the potential negative consequences of substance use, their initiation remains a significant public health concern. Considering substance use is often co-occurring with other psychiatric diagnoses, the current study examines whether and how impulsivity measures are associated with a ray of psychiatric disorders using behavioral and imaging data collected in the Adolescent Brain Cognitive Development (ABCD) study. We hypothesized that adolescents with one or more diagnoses and adolescents with more substance use history will show higher trait, response, and choice impulsivity in self report test and behavior tasks, respectively. Impulsivity was measured using Urgency- Premeditation- Perseverance- Sensation Seeking- Positive Urgency (UPPS-P), Stop Signal Task (SST) and Delay Discounting Task (DDT). Adolescents' psychiatric diagnosis and substance use history were assessed using a computerized version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) and Substance Use Interview from the ABCD study. Our preliminary analysis showed that in the current population (9-11 years old),

adolescents with externalizing diagnosis scored significantly higher on the UPPS-P test and were notably slower to respond to the stop signals in the SST, compared to healthy controls. Amount of substance use was positively correlated with the UPPS-P test score and the stop signal reaction time in youth. Altogether, our preliminary results identified relationships among impulsivity measures, psychiatric diagnosis, and substance use in preadolescents, which lays the foundational work for future analysis on distinct or common neurobiological underpinnings of these impulsivity forms adolescents.

Disclosures: Y. wang: None. **X. Xiao:** None. **Y. Yang:** None.

Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.18/A34

Topic: A.09. Adolescent Development

Support: Academy of Medical Sciences Newton Advanced Fellowship (NAF002/1001)
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UCT Division of Developmental Paediatrics, Department of Paediatrics and Child Health Masters Fellowship
Departmental research award from the UCT Department of Paediatrics and Child Health

Title: White matter microstructural changes in 6-year-old children who are HIV-exposed uninfected in a South African birth cohort - A Diffusion Tensor Imaging Study

Authors: *C. N. NYAKONDA[1,2], C. J. HENDRIKSE[2], C. J. WEDDERBURN[3,4], S. WILLIAMS[2], A. ROOS[5], N. HOFFMAN[6], D. J. STEIN[6], K. A. DONALD[2];
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Abstract: Objective: Magnetic resonance imaging (MRI) studies have described effects of in utero HIV exposure on children who are HIV-exposed uninfected (CHEU). This study aimed to investigate whether white matter microstructural differences previously observed in the Drakenstein Child Health study in 2-4-week-old CHEU compared to children not exposed (CHUU) persist in the same cohort at the age 6 years.
Methods: A total of 228 6-year-olds were invited for MRI, as part of a longitudinal nested neuroimaging study, of which 129 children (43 CHEU; 86 CHUU) had usable diffusion-weighted imaging (DWI) scans. DWI scans were pre-processed using TORTOISE software.

Multivariate analysis of variance models was conducted to assess group differences in diffusion parameters, adjusting for age at scanning, sex, height and prenatal smoking. Exploratory partial correlation analysis controlling for HIV exposure, assessed potential associations of diffusion parameters with cognition, measured using the Weschler Preschool and Primary Scale of Intelligence (WPPSI), and behaviour, measured with the Child Behaviour Checklist (CBCL).
Results: The CHEU group demonstrated lower axial diffusivity (AD) in the right posterior limb of the internal capsule, as well as lower mean diffusivity (MD) and radial diffusivity (RD) in the right inferior cerebellar peduncle compared to the CHUU group. Findings held on adjusting for covariates ($p<0.05$), but not false discovery rate correction. Right posterior limb internal capsule AD was negatively correlated with the WPPSI similarities score ($r= -0.198$, $p= 0.049$) and positively correlated with CBCL externalising subscale ($r= 0.212$, $p= 0.035$) and the CBCL aggressive behaviour subscale ($r= 0.249$, $p= 0.013$). Right posterior limb internal capsule MD and RD correlated with the CBCL somatic complaint's subscale score(MD: $r= 0.212$, $p= 0.035$; RD: $r= -0.208$, $p= 0.039$). Separately, AD and MD in the right inferior cerebellar peduncles correlated positively with the CBCL aggressive behaviour subscale.
Conclusion: White matter microstructure changes in the cerebellar region in this study are consistent with previously reported findings in neonates in the same cohort. While CHEU neonates showed alterations in the middle cerebellar peduncle, at 6 years CHEU showed alterations in the adjacent inferior cerebellar peduncle. Regional consistency of findings suggests the possibility of persistence of changes, and their association with CBCL subscale scores suggests that these may have clinical implications.

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Poster

PSTR100: Neuroimaging of the Human Adolescent Brain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.19/A35

Topic: A.09. Adolescent Development

Support: National Science Foundation (CAREER 11519520; BCS 1522986)
Raikes Foundation (61405837-118286)
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Stuart Foundation

Title: Exploring Meaning Making in Brain Network Patterns

Authors: *A. GHADERI[1], X.-F. YANG[2], R. GOTLIEB[3], D. L. JOHNSON[4], M. IMMORDINO-YANG[2];
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Abstract: During adolescence, youths develop the capacity to enrich their concrete, empathic and context-specific interpretations of social happenings with abstract, systems-level, and values-based considerations that transcend the situations at hand, a process we term transcendent thinking. We have previously shown that, while both concrete and transcendent thinking contribute to social functioning (Gotlieb et al., 2022), youths' proclivity to engage spontaneously in transcendent thinking during mid-adolescence predicted the development of functional brain networks, notably within the default-mode and executive control networks, which in turn, predicted identity development and life satisfaction later in life (Gotlieb et al., 2024). Here, we used longitudinal resting state fMRI data from 65 adolescents (aged 14-18 years at recruitment) across two sessions two years apart. On the day of the first session, participants also discussed their feelings about 40 minidocumentaries featuring other teens' compelling situations in a 2-hour private interview that was transcribed and coded for concrete and transcendent thinking. Participants' concrete and transcendent scores were uncorrelated. Modularity analysis classified participants into three groups: group 1 with low-mid transcendent/low-mid concrete scores, group 2 with low-mid transcendent/mid-high concrete scores, and group 3 with mid-high transcendent/mid-level concrete scores. Using the resting-state fMRI data, we evaluated five graph theoretical network measures at the whole-brain level [average connectivity weights (ACW), clustering coefficient (CC), characteristic path length (CPL), energy (H), and Shannon entropy (S)] and modular structure at the subnetwork level. Statistical analyses demonstrated significant group differences in all whole-brain network measures in the initial session, and linear models revealed divergent longitudinal trends in these whole-brain network measures across the 2-year interval. Subnetwork analyses revealed group modularity differences both in the initial data and in longitudinal change in the default-mode, salience, and sensorimotor networks. These findings suggest that adolescents' dispositions toward concrete and transcendent thinking in social contexts are related to their brain network development, and underscore the importance of capturing spontaneous thinking in ecologically valid tasks to appreciate sources of individual variability in the brain.

Disclosures: A. Ghaderi: None. **X. Yang:** None. **R. Gotlieb:** None. **D.L. Johnson:** None. **M. Immordino-Yang:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.01/Web Only

Topic: B.03. Ion Channels

Title: The effect of calcium ions on resting membrane potential

Authors: *E. ELLIOTT, R. L. COOPER;
Biol., Univ. of Kentucky, Lexington, KY

Abstract: Regulating membrane potential is key to cellular function. For many animal cells, the resting membrane potential is predominantly driven by a family of K2p (two-pore domain) potassium channels. These channels are commonly referred to as leak channels, as their presence results in the membrane being permeable to K^+ ions. These channels, along with various pumps and exchangers, keep cell resting membrane potential relatively close to potassium's equilibrium potential (E_K). However, in many cells, the resting membrane potential is more depolarized than the E_K due to a small Na^+ ion leak. Interestingly, raising $[Ca^{2+}]_O$ (extracellular Ca^{2+} concentration) can result in hyperpolarization of the membrane potential from the resting state. The mechanism for this hyperpolarization is not fully established. The effect may be due to calcium-activated potassium channels, Ca^{2+} ions' ability to block axonal voltage-gated Na^+ channels, and possibly Na^+ leak channels. Changing $[Ca^{2+}]_O$ from 0.5 to 3 mM hyperpolarizes the muscle. The mechanism appears to be the blockage of Na^+ leak channels. Substituting Li^+ or choline chloride for Na^+ did not significantly change the membrane potential, and the effect of increasing $[Ca^{2+}]_O$ still led to hyperpolarization. Replacing $CaCl_2$ with $BaCl_2$ resulted in depolarization. K2p channel overexpression in the larval muscle greatly reduced the effects of $[Ca^{2+}]_O$ on cell membrane potential, likely because it is heavily driven by the E_K in these muscles. These experiments provide an understanding of the mechanisms behind neuronal hypo-excitability during hypercalcemia, as well as the effect of altered expression of K2p channels on membrane potential.

Disclosures: E. Elliott: None. **R.L. Cooper:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.02/A36

Topic: B.03. Ion Channels

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Leo Foundation, Denmark, LF-OC-22-001114
Generalitat de Catalunya 2021SGR00292
Instituto de Salud Carlos III, Maria de Maeztu MDM-2017-0729 and CEX2021-001159-M

Title: Involvement of TRESK background potassium channel in modulating neuronal excitability and hippocampal synaptic plasticity

Authors: *H. LLUÍS[1,2], M. RADOSEVIC[3], J. LLIMÓS-AUBACH[1,2], A. CASTELLANOS[1,2,4], I. PALLÁS[1,2], A. P. PEREZ[1], G. CALLEJO[1,2], N. COMES[1,2], C. J. WIERENGA[5], X. GASULL[1,2];
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Biomedical Research (CRIB), University of Castilla-La Mancha, Ciudad Real, Spain; [5]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands

Abstract: To comprehend the brain's dynamic physiology, we must understand the mechanisms underlying neuronal excitability, crucial for neurons' electrical activation during synaptic communication. Of particular interest is controlled potassium current leakage via two-pore domain potassium channels which finely modulate the intrinsic excitability of neurons. TRESK, the latest discovered channel of the K2P family, has a well-characterized pivotal role in nociception. Intriguingly, it also exhibits widespread expression throughout the central nervous system, yet its function within the brain has remained unexplored. We are combining in-situ hybridization RNAscope technique and electrophysiology experiments to examine the contribution of TRESK to hippocampal excitability. We observed TRESK mRNA in excitatory and inhibitory neurons along the CA1-CA3 regions and dentate gyrus. Functionally, field potential and whole-cell patch-clamp recordings in acute slices revealed that TRESK knockout (KO) mice exhibit decreased paired-pulse facilitation and impaired long-term synaptic plasticity in the Schaffer Collateral pathway. Additionally, in the absence of TRESK, CA3 pyramidal neurons displayed enhanced excitability via reduced rheobase current and a tendency for a more depolarized resting membrane potential. Accordingly, there was an increased number of cells that were spontaneously active and they had higher firing frequencies compared to control slices. Our findings highlight the involvement of TRESK in neuronal hippocampal excitability and synaptic plasticity, which may explain the decreased spatial memory we observed in TRESK KO mice when conducting the novel object location test. In addition, we are currently exploring the role of TRESK in GABAergic cells and studying further the behavioral effects of its absence in the TRESK KO model while considering potential sex differences. These data serve as a foundation for future experiments to elucidate the role of TRESK channels in hippocampal intrinsic plasticity, which will provide insights into principles governing the dynamics of neural networks in memory formation.

Disclosures: H. Lluís: None. **M. Radosevic:** None. **J. Llimós-Aubach:** None. **A. Castellanos:** None. **I. Pallás:** None. **A.P. Perez:** None. **G. Callejo:** None. **N. Comes:** None. **C.J. Wierenga:** None. **X. Gasull:** None.

Poster

PSTR101: Other Ion Channels

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.03/A37

Topic: B.03. Ion Channels

Support: 1R35NS111600-01

Title: Photochemical interrogation of the operation of synaptic inhibition in dendrites

Authors: *S. DARVISH-GHANE;
Icahn Sch. of Med., Manhattan, NY

Abstract: The effect of neuronal inhibition on excitation has been a topic of long standing interest for physiologists. Notably, in the twentieth centaury Sherrington won his Nobel Prize for "Inhibition as a Coordinative Factor", which went on to be a subject of study for Bernard Katz. Subsequently, Wilfred Rall produced highly influential mathematical models of the electrical properties of neurons, deriving the so-called "cable equation" of dendritic conduction. Application of this lead to the important conclusion that inhibitory inputs are most effective in veto of excitation when they occur between excitation and the cell soma (i.e. "on path"). Recent studies by Segev and colleagues (Neuron 2012, 2020) have extended Rall's ideas, suggesting that "off path" inhibition could be very effective in the modulation of excitation. The challenge in trying to test such hypotheses is we lack the ability for rapid, localized, independent application of glutamate and GABA to dendrites in an arbitrarily patterned, facile way. Recently, we introduced two new caged neurotransmitters (Angew. Chem. 2024, e202315726) which can be photolyzed with excellent chromatic selectively using violet and green light. These wavelengths are optically compatible with modern two-photon microscopes. Now, we have made second-generation versions of these probes, by addition of polyethyleneglycol units, in order to improve their solubility in ACSF. These probes allowed us to test the ideas advanced by Segev's modeling, and show that two-color uncaging of glutamate and GABA using violet and green is highly effective on neurons in acutely isolated brain slices.

Disclosures: S. Darvish-Ghane: None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.04/A38

Topic: B.03. Ion Channels

Title: High-throughput Functional Characterization of Piezo Channels in Human Induced Pluripotent Stem Cell-Derived Sensory Neurons Using Automated Patch Clamp Systems

Authors: V. TRUONG[1], A. RANDOLPH[2], Y.-L. LU[2], R. CERONE[2], *A. OBERGRUSSBERGER[3], **E. DRAGICEVIC**[3], R. HAEDO[2], T. STRASSMAIER[2], P. WALSH[1]; [1]Anatomic Inc., Minneapolis, MN; [2]Nanion Technologies Inc., Livingston, NJ; [3]Nanion Technologies GmbH, Munich, Germany

Abstract: Piezo channels are crucial mechanosensitive ion channels that play a vital role in sensing mechanical stimuli in various cell types, including sensory neurons. Developing a high-throughput model to study these channels using human induced pluripotent stem cell (hiPSC) sensory neurons offers a promising pathway to accelerate research into mechanotransduction and enable high-throughput screening of drugs, potentially accelerating the discovery of treatments

for sensory disorders. We have previously shown that human induced pluripotent stem cells (hiPSCs) can be rapidly differentiated into highly pure populations of sensory neurons (RealDRG) using small molecules and growth factors, and that these cell types are transcriptionally similar to primary human tissues via bulk RNA sequencing. In this study, we looked to functionally characterize the Piezo mechanosensitive ion channels expressed in RealDRG. Utilizing calcium imaging, we show that the neurons respond to Yoda1 as early as two weeks in culture. In order to develop a more high-throughput assay amenable for screening, we dissociated RealDRG at 14, 21, and 28 days in culture and applied the M-Stim protocol to electrophysiologically characterize Piezo channels on the SyncroPatch automated patch clamp system in 384 well plate format. The M-Stim protocol involves 3 rounds of stimulation with external buffer alone. Following this, a fourth application of buffer plus the Piezo1 selective potentiator, Yoda1, and a fifth application of buffer with $GdCl_3$ as a control blocker of Piezo channels are applied. We found that RealDRG neurons had similarities in activation and inactivation kinetics to Piezo1 expressing HEK cells. Together, these findings demonstrate the ability functionally screen potential new modulators of mechanosensitive ion channels in human sensory neurons in high throughput systems.

Disclosures: V. Truong: A. Employment/Salary (full or part-time):; Anatomic Incorporated. **A. Randolph:** A. Employment/Salary (full or part-time):; Nanion Technologies, Inc. **Y. Lu:** A. Employment/Salary (full or part-time):; Nanion Technologies, Inc. **R. Cerone:** A. Employment/Salary (full or part-time):; Nanion Technologies Inc. **A. Obergrussberger:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **E. Dragicevic:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **R. Haedo:** A. Employment/Salary (full or part-time):; Nanion Technologies, Inc. **T. Strassmaier:** A. Employment/Salary (full or part-time):; Nanion Technologies Inc. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.05/A39

Topic: B.03. Ion Channels

Title: Utilising Solid Supported Electrophysiology (SSME) to accelerate discovery of TRPML1 modulators.

Authors: A. BIZIOR[1], E. MALONE[1], J. KEWNEY[2], *P. MADAU[2], D. DALRYMPLE[2]; [1]Screening, [2]SB Drug Discovery, Glasgow, United Kingdom

Abstract: Neurodegenerative disorders such as Alzheimer's and Parkinson's disease remain conditions with major unmet clinical needs. Abnormalities in the endosomal-autophagic-lysosomal system, progressive neurological dysfunction and regional neuronal loss constitute their common characteristics. Transient receptor potential mucolipin 1 (TRPML1) is a well-

known, non-selective cation channel of the endolysosomal system that can transport Ca^{2+}, Fe^{2+} and Zn^{2+}. There is a strong connection between endolysosomal TRPML1 dysfunction and neurodegenerative disorders, thought to be a result of its importance in controlling calcium signalling and homeostasis of lysosomes, autophagy, and modulation of oxidative stress. Therefore, modulation of TRPML1 presents a promising strategy to improve the function of neurons impacted by neurodegenerative disorders by increasing autophagy and promoting the clearance of protein aggregates and reactive oxygen species (ROS) build-up. Numerous platforms offer insights into TRPML1 function and pharmacology, however, lack of specific tools allowing for investigation of TRPML1's role in pathological processes are still obstacles for drug discovery. Solid Supported Membrane Electrophysiology (SSME) present a novel high throughput method to resolve this challenge. Using enriched lysosomal fractions from recombinant HEK cell lines expressing TRMPL1 we have successfully developed SSME assays, using both SURFE^{2}R N1 (single sensor) and SURFE^{2}R 96SE platforms to investigate TRPML1's cation selectivity and pharmacology. Both platforms show excellent reproducibility and platform-to-platform correlation. SSME allows investigation of TRPML1 activity and response to drugs in its native environment without the need for continuous cell culture. In conjunction with other technologies, SSME technology facilitates reliable high- throughput compound screening, enabling discovery of novel TRPML1 modulators and aiding the advancement of knowledge of TRPML1 and its role in normal physiology and disease.

Disclosures: A. Bizior: None. **E. Malone:** None. **J. Kewney:** None. **P. Madau:** None. **D. Dalrymple:** None.

Poster

PSTR101: Other Ion Channels

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.06/A40

Topic: B.03. Ion Channels

Support: NIMH 1RO1MH085724-01
NIMH 5T32MH019113-22

Title: Acidic extracellular pH excites cerebellar Purkinje neurons through ASIC1A

Authors: *J. B. HARDIE[1], J. B. WEMMIE[2];
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Abstract: The cerebellum is critical for cognition as well as motor learning and is increasingly recognized as an important site of dysfunction in a number of neurological illnesses. While pH abnormalities in cerebellum have been reported in a variety of neuropsychiatric illnesses, little is known about how pH affects cerebellar neuron activity. Purkinje cells (PCs) provide the sole axonal output of the cerebellar cortex and are thus critical for cerebellar function. Here, we explored how extracellular acidosis might impact these neurons. In acute brain slices, we found

that application of extracellular acid (pH 6.5) evoked depolarizing potentials and increased spontaneous action potential firing in PCs. Because many excitatory cation channels and receptors are inhibited by acid, we hypothesized this excitatory response may be unique to a specific source of conductance. A leading candidate is the acid-sensing ion channel ASIC1A, which is permeable to Na^+ and Ca^{2+} and activated by extracellular acidosis. We tested this hypothesis by disrupting ASIC1A and found that both acid-evoked increases in action potential frequency and depolarization in PC dendrites were absent in *Asic1a*$^{-/-}$ mice. Because ASIC1A is also permeable to Ca^{2+}, we next tested Ca^{2+} responses with fluorescent imaging. We found that extracellular acidosis evoked robust Ca^{2+} responses in PC dendrites in wild-type mice, and that these responses were abolished by ASIC1A disruption. Importantly this deficit in dendritic Ca^{2+} responses was specific to extracellular acidosis because extracellular glutamate (pH 7.4) produced normal Ca^{2+} responses in *Asic1a*$^{-/-}$ mice. Because elevations in extracellular glutamate can be accompanied by acidosis, for example during ischemic conditions, we wondered how combining these two stimuli would affect PC activity. Interestingly, in wild-type mice Ca^{2+} responses evoked by glutamate at pH 5.6 were very similar to those evoked by glutamate at pH 7.4. Whereas in *Asic1a*$^{-/-}$ mice, responses to glutamate at pH 5.6 were significantly reduced compared to those evoked by glutamate at pH 7.4. Together, these observations suggest that extracellular acidosis can excite cerebellar PCs through ASIC1A, and that the ASIC1A-mediated effects can compensate or override inhibitory effects of acidic pH on other sources of Na^+ and Ca^{2+} influx. We speculate these findings may have important implications for pathological states accompanied by cerebellar acidosis.

Disclosures: J.B. Hardie: None. **J.B. Wemmie:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.07/A41

Topic: B.03. Ion Channels

Support: Milken Institute BD-0000000063

Title: A Novel Mitochondrial Target as Therapeutic Approach to Bipolar Disorder

Authors: *L. SHEN[1], J. KIM[2], Y. ZHANG[3], L. K. KACZMAREK[3], I.-H. PARK[2], H. BLUMBERG[4], E. A. JONAS[1];
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Abstract: Neurons derived from patient-induced pluripotent stem cells, (iPSCs) have been used to model neuropsychiatric disorders. Stem cell-derived 3D human brain organoids have the potential to recapitulate features of the human brain with greater complexity than 2D models and

are increasingly being applied to model diseases affecting the central nervous system. Studies of hippocampal dentate gyrus-like neurons derived from patients with bipolar disorder have previously revealed mitochondrial abnormalities and neuronal hyperexcitability compared with healthy controls (HCs).Our lab had shown that neurons from a bipolar disorder model (patient cells) have an imbalance of ATP synthase components. The membrane embedded portion of the ATP synthase (c-subunit ring) was found to be overexpressed compared to the assembled ATP synthase and this contributed to formation of a leaky channel in mitochondrial membranes. From electron microscopic images, we also found BD neurites and somata have altered mitochondria. Our mitochondrial recordings show changes consistent with mitochondrial abnormalities.We hypothesize that mitochondria are abnormal in BD neurons. Our findings may indicate a link to brain energy changes that could be caused by differences in cellular metabolism.

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Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: B.03. Ion Channels

Support: NIH NINDS - 1F99NS134140-01
NIH NINDS -R01 NS113499
NIH NINDS -NS113499-S1

Title: Kir4.1 mediates activity-induced astrocyte depolarization initiation and spatial propagation

Authors: *J. P. GARCIA[1], M. ARMBRUSTER[2], C. G. DULLA[3];
[1]Tufts Univ., Boston, MA; [2]Neurosci., Tufts Univ., Boston, MA; [3]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Astrocytes interact with synapses through their distal processes enriched with proteins mediating glutamate and potassium (K^+) uptake. Although neuronal activity increases $[K^+]_e$, depolarizing astrocytes, changes in V_m have generally been considered small. To address this challenge, we previously expressed genetically encoded voltage indicators (GEVIs) in astrocytes and demonstrated large, rapid, focal, and pathway-specific depolarizations in peripheral astrocyte processes (PAPs) during neuronal activity. Kir4.1, an inwardly rectifying K^+ channel expressed heavily by astrocytes, is implicated in multiple neurological and psychiatric disorders. Here we aim to understand the role of Kir4.1 in astrocyte electrical activity. We hypothesized that Kir4.1 plays a role in astrocyte depolarization after neuronal activity and helps dissipate extracellular K^+ challenges via spatial propagation. Using astrocyte GEVIs, we saw that blocking Kir4.1 with Ba^{2+} significant increases in GEVI $\Delta F/F_0$, suggesting that Kir4.1-medicated K^+ influx helps minimize activity-dependent PAP depolarization. Surprisingly, our data shows that blocking

Kir4.1 with Ba^{2+} significantly speeds up astrocyte repolarization after neuronal activity. Because Ba^{2+} can have off-target effects, we conditionally deleted Kir4.1 in astrocytes using a $Kir4.1^{fl/fl}$ mouse model and an astrocyte specific Cre-virus. We saw a similar speeding up of astrocyte membrane potential repolarization after neuronal activity. We next performed high-magnification, high-speed GEVI imaging to identify hot-spots of astrocyte depolarization that we suspect occur at sites of synaptic activity, Interestingly, we found the astrocyte repolarization was identical in WT and Kir4.1 cKO or Ba^{2+}. Outside of hot-spots WT repolarization is much slower than Ba^{2+} or cKO of Kir4. Together, this suggests that Kir4.1 helps astrocytes spatially propagate depolarization and provides extracellular regulation of K^+ concentration. We were then interested in determining sources of K^+ leading to depolarization. Dendrotoxin, a selective inhibitor of Kv1.1 channels specifically localized to the presynaptic terminals, reduced PAP depolarization. This is consistent with a presynaptic source of K^+ driving astrocyte depolarization rather than postsynaptic K^+. This would represent a novel form of astrocyte electrical activity and suggests a previously unanticipated role for Kir4.1 in shaping K^+ dynamics on a nanoscale. Future studies will focus on how Kir4.1 mediates the propagation of astrocyte depolarization and how it may contribute to shaping neuronal activity via glutamate transporters and other mechanisms.

Disclosures: J.P. Garcia: None. **M. Armbruster:** None. **C.G. Dulla:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.09/A43

Topic: B.03. Ion Channels

Support: NSERC
CIHR

Title: Anandamide transport by Pannexin-1 may modulate local circuits in the hippocampus

Authors: *L. AU, C. ANDERSON, R. J. THOMPSON;
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Abstract: Pannexin-1 channels (Panx1) are pivotal in cellular signaling. However, the gating mechanisms of this channel and their involvement in neuronal plasticity are largely unknown. We recently discovered that Panx1 can rapidly shift from anion permeable to anandamide transport and this depends on the N-terminal helix (NTH). Our group reported that Panx1 block increases anandamide (AEA) concentrations in hippocampal slices and induces seconds-long presynaptic glutamate release via TRPV1 channels. Here, we investigated how these distinct gating modalities of Panx1 contribute to neuronal plasticity. Deletion of the NTH locked Panx1 into an AEA-permeable state as evident by loss of ionic currents and increased uptake of the fluorescent AEA derivative, CAY10455. We hypothesize that modulating the NTH domain of

Panx1 regulates AEA concentrations in vivo. By using adeno-associated virus (AAV)-mediated expression of dominant negative ΔN20-Panx1 in hippocampal CA1 pyramidal cells, synaptic plasticity in acute hippocampal brain slices was examined. To further assess the physiological significance of Panx1 NTH gating in presynaptic plasticity, we acutely blocked Panx1 channels in hippocampal slices from Thy1/GCaMP6f mice while providing Shaffer Collateral stimulation to induce glutamate bursting. We hypothesize that increased AEA concentrations resulting from ΔN20-Panx1 or pharmacological block of Panx1 leads to local synchrony of local clusters of CA1 pyramidal neurons. To elucidate the role of Panx1 NTH in this process, in vivo GCaMP6f imaging was recorded in cells expressing ΔN20-Panx and pyramidal neuron synchronicity was assessed.

Disclosures: L. Au: None. **C. Anderson:** None. **R.J. Thompson:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.10/A44

Topic: B.03. Ion Channels

Support: NIMH Grant 1R01MH113986
CFF & UTHSC Grant 002544I221

Title: Neuronal acid-sensing ion channel 1a regulates neuron to glioblastoma synapses

Authors: *G. PARK[1], Z. JIN[2], J. DU[1];
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Abstract: Glioblastoma (GBM) is one of the most lethal malignancies of the central nervous system (CNS), infiltrating and disrupting brain structure and function. Despite intensive research efforts, GBM survival has not changed significantly over the past two decades, indicating an urgent need to develop novel therapeutic strategies. Recent research suggests that neuronal activity may be a potential therapeutic target for GBM. Neuronal activity promotes GBM progression via secreted proteins and neuron-to-GBM synapses, and GBM cells boost neuronal activity to further reinforce the malignant cycle. Whereas strong evidence supports that the activity of neuron-to-GBM synapses accelerates GBM progression, the molecular mechanisms that modulate the formation and function of neuron-to-GBM synapses remain largely unknown. Our recent findings suggest that a proton (H^+) signaling pathway actively mediates neuron-to-GBM synaptic communications by activating acid-sensing ion channel 1a (ASIC1a), a predominant neuronal H^+ receptor. Supporting this idea, our preliminary data revealed that 1) local acid puff on neurons in GBM-bearing brain slices induces postsynaptic currents of GBM cells; 2) stimulating ASIC1a$^{-/-}$ neurons induces smaller AMPA receptor dependent postsynaptic currents in GBM cells than stimulating wild-type (WT) neurons; 3) GBM-bearing ASIC1a$^{-/-}$

mice exhibited reduced tumor size and survived longer than the GBM-bearing WT mice; 4) pharmacologically targeting neuronal ASIC1a inhibited GBM progression. In summary, uncovering the cellular and molecular mechanisms by which H+ mediates neuron-to-GBM synapses is very important, especially as it relates to tumor progression in the brain. The outcomes of this project will greatly expand our understanding of how this deadly tumor integrates into the neuronal microenvironment. Moreover, elucidation of this mechanism would further facilitate the development of new therapeutic targets for preventing tumor invasion in the brain, in which most of the currently available therapeutics for presently lethal brain cancers are not satisfied.

Disclosures: G. Park: None. **Z. Jin:** None. **J. Du:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.11/A45

Topic: B.03. Ion Channels

Support: JSPS KAKENHI Grant-in-Aid for Early-Career Scientists 20K17839
JSPS KAKENHI Grant-in-Aid for Early-Career Scientists 17K16731

Title: Involvement of TRPM4 ion channels in mouse temperature sensing

Authors: *R. NISHIMOTO[1], M. TOMINAGA[2];
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Thermal Biol. Res. Group Nagoya Advanced Res. and Develop. Ctr., Nagoya City Univ., Nagoya, Japan

Abstract: Background Understanding temperature sensing is vital for both behavioral adjustments and cellular functions. Our research explores how temperature variations affect cellular physiology, aiming to uncover the molecular mechanisms behind neuroprotection in therapeutic hypothermia. Specifically, we focus on the thermosensitive transient receptor potential (TRP) channel. Among them, TRPM4, found as a calcium-activated TRP channel, has been reported for its thermosensitivity (Talavera K *et al* 2005 Nature), but it is still controversial. Furthermore, the involvement of TRPM4 in temperature sensing has not been investigated. Here, we present our findings on TRPM4 thermosensitivity and its involvement in mouse temperature preference using *Trpm4*-knockout (TRPM4KO) mice. **Methods** To characterize TRPM4 thermosensitivity, whole-cell patch clamp experiments were conducted using mouse TRPM4-expressing HEK293T cells. For TRPM4 channel activation, we utilized 1μM intracellular free calcium. Additionally, we assessed the involvement of TRPM4 in mouse temperature preference behavior using TRPM4-knockout (TRPM4KO) mice, generated via CRISPR/Cas9 gene editing (Vennekens et al., 2007 Nat Immunol). The test involved a two-temperature choice (25°C vs 25°C, 25°C vs 35°C, 25°C vs 45°C) on a variable temperature hot plate. The littermates of wild-type (WT) and TRPM4KO (male, 5-7 weeks old) were included. Time spent in each temperature

zone during 10 minutes of free movement was recorded in seconds and analyzed (ANOVA, Tukey test, $p<0.05$). **Results** In the patch clamp experiments, heat application induced large currents with strong outward rectification in mouse TRPM4-expressing HEK293T cells after desensitization of calcium-activated currents with intracellular free Ca^{2+}, while heat-evoked currents were not observed without intracellular free Ca^{2+}. In the temperature preference tests, WT (N=7), TRPM4(+/-) (N=11), and TRPM4(-/-) (N=16) were included. Time spent in the test plate was (sec); at 25°C: WT=308 ± 50, (+/-)=232 ± 33, (-/-)=301 ± 32, at 35°C: WT=349 ± 51, (+/-)=297 ± 36, (-/-)=293 ± 54, at 45°C: WT=144 ± 53, (+/-)=168 ± 32, (-/-)=227 ± 47. WT and TRPM4(+/-) mice spent significantly less time at 45°C compared to 25 and 35°C (P=0.017 and 0.03, respectively), while TRPM4(-/-) mice did not exhibit such behavior (P=0.43). **Conclusion** Our findings suggest that 1) TRPM4 can be activated by heat, requiring a high concentration of intracellular calcium and 2) TRPM4KO mice displayed no aversion to higher temperatures, indicating that TRPM4 may be involved in temperature sensing.

Disclosures: R. Nishimoto: None. **M. Tominaga:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.12/A46

Topic: B.03. Ion Channels

Support: NS113991
NS128543

Title: Localization of AP2α2, TRPV1 and PIEZO2 to the Large Dense Core Vesicles of Human Dorsal Root Ganglion Neurons

Authors: O. JOSHI[1], R. G. POWELL[2], M. MARTIN[3], ***A. BHATTACHARJEE**[4]; [1]State Univ. of New York, Univ. at Buffalo, Amherst, NY; [2]Boston Children's Hosp., Boston, MA; [3]Neurosci., State Univ. of New York, Buffalo, Buffalo, NY; [4]SUNY-Buffalo, Buffalo, NY

Abstract: Dorsal Root Ganglia (DRG) consist of both peptidergic and non-peptidergic nociceptive neurons. CGRP, an inflammatory neuropeptide, is a classical marker of peptidergic nociceptors and CGRP is stored within the large dense core vesicles (LDCVs) of these neurons. In addition to storing large peptide neurotransmitters, LDCVs might also serve to transport key membrane proteins to the peripheral terminals. This immunohistochemical study investigated the localization of different membrane proteins to the LDCVs of human DRG neurons. Validated antibodies against the endocytotic subunit AP2α2, the heat-activated channel TRPV1 and the mechanosensitive channel PIEZO2 were used in conjunction with an antibody against CGRP on sections of intact human DRG isolated from de-identified human subjects. High magnification confocal microscopy was used to determine the co-localization signal of these membrane proteins with CGRP. We observed a strong co-localization of AP2α2 with the CGRP containing

LDCVs signifying its role in membrane recycling. Moreover, we also observed a strong colocalization of TRPV1 and PIEZO2 and with CGRP suggesting that LDCV release controls the trafficking of these channels to the membrane. It is likely that during injury, a bulk exocytosis of CGRP will concomitantly increase the surface expression of TRPV1 and PIEZO2 channels enhancing the responsiveness of these neurons to nociceptive stimuli. Therefore we hypothesize that neurons that co-localize TRPV1 and PIEZO2 to CGRP containing LDCVs are likely silent nociceptors.

Disclosures: O. Joshi: None. **R.G. Powell:** None. **M. Martin:** None. **A. Bhattacharjee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Channavix Therapeutics, LLC, Mimetic Medicines, INC.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.13/A47

Topic: B.03. Ion Channels

Support: R01MH120637
F31MH131358

Title: Novel brain-penetrant HCN inhibitors to treat stress susceptibility

Authors: E. TEICHMAN[1], S. E. MONTGOMERY[2], ***M. CAROLE**[3];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Modendo, Icahn Sch. of Med. at Mount Sinai, Boulder, CO; [3]Icahn Sch. of Med., New York, NY

Abstract: Establishing rapid and long-lasting antidepressant effects is the main challenge of the current treatment strategies and drug discovery efforts. In this study, we demonstrate that newly designed compounds to inhibit brain HCN channels, yield potent therapeutic effects and alleviate stress-induced social, reward, and cognitive deficits - hallmarks of major depressive disorders. This is a highly novel finding as very few research efforts have improved the blood-brain barrier permeability of HCN channel inhibitors, and thereby, restored dopamine neuron activity through modulation of their intrinsic properties.Leveraging a mouse model of chronic social stress to capture behavioral features of MDD, we highlight the hyperpolarization-activated cyclic nucleotide-gated channels (HCN), as a key regulator of dopamine neuronal functions and resulting behavioral disturbances. Our multilevel electrophysiological approach shows that the new compounds **rapidly** reduce ventral tegmental area dopamine neuron hyperactivity induced by stress. We further established that the top two new compounds have improved **brain bioavailability** compared to the parent compound Cilobradine. Importantly, these studies were recapitulated in female mice. Lastly, we establish that a single systemic injection of our novel HCN inhibitor holds a **prolonged therapeutic** efficacy on stress-induced social, reward, and

cognitive impairments. Our results provide a roadmap of how to investigate and exploit the influence of ion channels on complex brain disorders as well as a HCN inhibitor compound series for future studies.

Disclosures: E. Teichman: None. **S.E. Montgomery:** None. **M. Carole:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.14/A48

Topic: B.03. Ion Channels

Title: Divergent electrophysiological and morphological properties of the paraventricular nucleus between the common marmoset and mouse

Authors: *J. SUNSTRUM[1], S. MESTERN[2], S. EVERLING[3], J. C. MARTINEZ-TRUJILLO[4], W. INOUE[2];
[1]Neurosci., [3]Physiol., [2]Western Univ., London, ON, Canada; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, Schulich Sch. of Med. and Dentistry, Western Inst. for Neuroscience, Western Univ., London, ON, Canada

Abstract: Understanding how rodent physiology differs from primates is vital to informing human neuropsychiatric conditions. The set of coordinated physiological adaptations representing the mammalian stress response are considered highly conserved across species. However, the biophysical properties of the paraventricular hypothalamic nucleus (PVN) neurons responsible for this have exclusively been studied in rodents. The expansion of upstream input regions and altered history of stress-related evolutionary pressures likely changed the pattern of input received by hypothalamic neurons. Accordingly, there may be primate-specific adaptations to PVN neurons that are vital to understanding human stress neurophysiology. Here, we've conducted the first comprehensive analysis of primate PVN using the common marmoset (Callithrix jacchus) and collected a dataset of 392 neurons (N=30; age=1-10 years; 15 female) and compared them to their mouse counterparts (n=174; N=37; age=3-24 months; 21 female) using patch clamp electrophysiology in acute brain slices, combined with post-hoc morphology reconstruction, immunohistochemistry and *in situ* hybridization. At the cell subtype level, the characteristics that are used to classify the major PVN subtypes in rodents matched the spectrum of cells found in marmoset PVN. However, species-specific features were found within neuron subtypes. Marmoset parvocellular neurons had slower passive membrane properties and reduced excitability relative to mice, indicative of changes in the temporal summation of inputs. Morphologically, marmoset parvocellular neurons were larger and had increased spine density, which may suggest an altered pattern of input. Intriguingly, these neurons also exhibited substantially larger voltage sag, a key feature indicative of the expression of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Blocking HCN channels further increased the time constant and promoted synaptic summation of excitatory input leading to increased

spontaneous and evoked action potential frequency. Enhancing HCN with cAMP modulators (8-Bromo-cAMP, 5-HT) lowered the input resistance and time constant and dampened EPSP summation, indicating HCN channels subserve state-dependent modulation of synaptic integration. Overall, marmoset parvocellular neurons have an added layer of computation, whereby regulation of HCN channels by neuromodulators allows for dynamic control of the time window for synaptic integration. These distinct features of marmoset PVN neurons may reflect fundamental differences in synaptic integration adaptive for the lifestyle and stressors of primates.

Disclosures: J. Sunstrum: None. **S. Mestern:** None. **S. Everling:** None. **J.C. Martinez-Trujillo:** None. **W. Inoue:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.15/A49

Topic: B.03. Ion Channels

Support: NSFC

Title: The different roles of the PAC channel in the central nervous system and peripheral nervous system in the regulation of pain

Authors: J. GAN[1], X. XU[1], J. JUNWEI[1], Q. TANG[2], ***Z. ZHANG**[1];
[1]Xuzhou Med. Univ., Xuzhou, China; [2]Jiangsu Province Key Lab. of Anesthesiol.,, XuZhou, China

Abstract: PAC channels are proton-activated chloride channels, encoded by TMEM206 genes, which not only exhibit acid-activation properties but also show voltage-dependency, temperature-sensitivity, and halogen anions permeability. PAC channels are widely expressed in the nervous system and play an essential role in ischemia. But its role in nociceptive perception remains unknown. In this study, we investigated the role of the PAC channel in pain perception using PAC channel-deleted mice, a combination of CaMKII-cre virus, Advillin-Cre, and TMEM206-Floxed mice. We found that the global $PAC^{-/-}$ and $Advillin^{+/Cre}PAC^{-/-}$ mice exhibited decreased hot pain, cold pain, mechanical pain, and neuropathic pain. In addition, we found that in the chronic constriction injury (CCI) model mice, the c-fos expression in the $PAC^{-/-}$ mice is greatly decreased in the IS, PVC, and CeA nucleus, compared to the WT mice. PVC-specific deletion of the PAC channel in mice causes increased neuropathic pain threshold in CCI model mice but fails to alter the sensitivity to heat, cold, and noxious mechanical stimuli in the mice without CCI. These results suggest the different roles between the PAC channel expressed in the central nervous system and the PAC channel in the peripheral nervous system.

Disclosures: J. gan: None. **X. Xu:** None. **J. Junwei:** None. **Q. Tang:** None. **Z. Zhang:** None.

Poster

PSTR101: Other Ion Channels

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.16/A50

Topic: A.07. Developmental Disorders

Support: University of Dayton Honors Program
Lancaster-McDougal award, Department of Biology, University of Dayton

Title: Conditional Hemizygous Deletion of SERCA2 in the Brain's GABAergic Neurons does not Significantly Impact Behavior

Authors: *H. N. OTT, B. KLOCKE, S. ISTENES, M. ROACH, P. M. PITYCHOUTIS;
Dept. of Biol., Univ. of Dayton, Dayton, OH

Abstract: Calcium ions (Ca^{2+}) comprise critical ionic and intracellular second messengers that regulate a variety of important neuronal processes including neurotransmitter release, apoptosis and synaptic plasticity. Notably, dysfunction of Ca^{2+} homeostasis in the brain has been implicated in the pathophysiology of both neurodegenerative (i.e., Alzheimer's, Parkinson's, and Huntington's diseases) and neurodevelopmental disorders (i.e., autism-spectrum disorder, attention-deficit hyperactivity disorder, and schizophrenia). The sarco/endoplasmic (SR/ER) reticulum Ca^{2+} ATPase 2 (SERCA2) is an integral Ca^{2+}-handling protein pump that is ubiquitously expressed in neurons and responsible for maintaining intracellular Ca^{2+} homeostasis by sequestering Ca^{2+} ions into the ER. Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the brain and is synthesized by glutamate in the context of a single-step reaction catalyzed by two isoforms of the enzyme glutamic acid decarboxylase (GAD) (i.e., GAD67; *Gad1* and GAD65; G*ad2*) that are co-expressed in most GABAergic interneurons. Importantly, GABAergic neuronal function has been widely implicated in behavioral regulation. In the context of the current study, we employed a *Cre-loxP* conditional genetic mouse model approach to assess the effects of the targeted developmental deletion of *Serca2* in the brain's *Gad2*$^{+}$ neurons in important behavioral domains including locomotor activity (open field test), spatial working memory (Y-maze), anxiety (dark/light box test), and depressive-like behavior (splash test and forced swim test; FST). Notably, different rounds of breeding did not yield any viable *Serca2*$^{lox/lox}$*;Gad2*$^{Cre/0}$ pups, indicating that developmental conditional biallelic deletion of *Serca2* in this specific GABAergic neuronal sub-population is embryonically lethal. Interestingly, behavioral reactivity upon hemizygous SERCA2 deletion in adult male and female *Serca2*$^{lox/WT}$*;Gad2*$^{Cre/0}$ mice (N=10-12) was not statistically significantly different from their control *Serca2*$^{lox/lox}$*;Gad2*$^{0/0}$ counterparts (N=6-9). Taken together, our findings highlight the critical importance of SERCA2 in maintaining intracellular Ca^{2+} homeostasis in $GAD2^{+}$ positive GABAergic neurons and its impact on neurodevelopmental processes. Most importantly, our data further indicate that the *Serca2* gene may operate in a haplosufficient manner in these neurons, as a single functional *Serca2* allele results in a normal phenotype in the behavioral domains assessed.

Disclosures: H.N. Ott: None. **B. Klocke:** None. **S. Istenes:** None. **M. Roach:** None. **P.M. Pitychoutis:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.01/A51

Topic: B.05. Synaptic Plasticity

Support: Australian Research Council Discovery Project

Title: Alternative splicing regulation in neuronal homeostatic plasticity

Authors: *M. RAHMAN, V. ANGGONO, J. WIDAGDO;
Queensland Brain Inst., The Univ. of Queensland, Brisbane, Australia

Abstract: Constant perturbations in neuronal activities can elicit a detrimental outcome to neuronal circuits. Neurons sense and evoke homeostatic response during perturbation, requiring cell-wide adjustments that rely on transcriptional and mRNA translational programming. Alternative splicing (AS) of mRNA variants is a major driver of neural specification and synaptic plasticity, giving rise to an enormous repertoire of neuronal proteomes, yet its role in homeostatic plasticity has received little attention. In our study, we induced homeostatic *synaptic scaling* in primary mouse cortical neurons by chronic inactivation with tetrodotoxin (TTX) for 24 hours, which leads to the scaling up of glutamate receptors in the neurons. RNA-seq analysis of chronically inactivated neurons compared to vehicle-treated control neurons, followed by differential AS analysis revealed >800 skipped exon events, >100 alternative 5' and 3' splice site events, 94 mutually exclusive events, and ~150 retained introns significantly modulated by TTX treatments (difference in percent spliced in, ΔPSI > 10%; FDR < 0.05). Overall, differentially spliced genes are associated with synapse organisation and regulation of RNA splicing itself. These data provide precedence for our ongoing investigation, shedding light on the role of AS regulation as a basis of neuronal homeostasis.

Disclosures: M. Rahman: None. **V. Anggono:** None. **J. Widagdo:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.02/A52

Topic: B.05. Synaptic Plasticity

Support: K01 MH129760

Title: The Crucial Role of HEXIM1 in Modulating P-TEFb-Induced Immediate Early Gene Expression in Neurons

Authors: *M. HTET[1], C. S. ESTAY[1], B. E. POWERS[2], G. A. KAAS[3], R. J. COLBRAN[4], C. B. GREER[1];
[1]Mol. Neurosci. & Pharmacol., Loyola Univ. Chicago, Maywood, IL; [2]Res. Service, Loyola Univ. Chicago, Hines, IL; [3]Pharmacol., Vanderbilt Univ. Med. Ctr., Nashville, TN; [4]Dept Molec Physiol & Biophysics, Vanderbilt Univ. Sch. Med., Nashville, TN

Abstract: Rapid and transient activation of gene expression in neurons is essential for the synaptic plasticity underlying learning and memory. Many genes amenable to quick activation in neurons exist in a poised transcriptional state where RNA polymerase II (RNAP2) initiates transcription but pauses just downstream of the gene promoter. Studies have shown altered RNAP2 pausing is implicated in long term memory deficits. Upon neuronal depolarization, the paused RNAP2 is released, allowing completion of mRNA synthesis, a process mediated by the positive transcription elongation factor b (P-TEFb) protein heterodimer. Under baseline conditions, P-TEFb is sequestered in a large inactive protein complex containing Hexamethylene bisacetamide inducible protein 1 (HEXIM1). Stimuli that induce gene expression dissociate HEXIM1 from P-TEFb, allowing P-TEFb to release the paused RNAP2 and initiate transcriptional elongation. Importantly, we found that HEXIM1 physically interacts with P-TEFb in the brain and in cultured neurons. Inhibiting transcriptional elongation with P-TEFb inhibitors decreased *Fos, Egr1, Arc* and *Nr4a2* induction by KCl stimulation in cultured neurons. Treatment of cells with HMBA has been reported to dissociate P-TEFb from the HEXIM1 inhibitory complex. Therefore, we examined the effect of HMBA on immediate early gene (IEG) expression, and observed overall increased IEG expression in the absence of stimulation, and decreased induction by KCl. Following up on this finding, we are generating a system to rapidly degrade HEXIM1 so we can observe the effects of P-TEFb disinhibition directly both *in vitro* and *in vivo*. We also show that stimulation of mouse primary cortical and hippocampal neurons using KCl induces IEG expression, but subsequent stimuli temporarily suppress the activation of some, but not all, IEGs. During this transcriptional refractory period, *Hexim1* mRNA levels are increased, while HEXIM1 protein levels are reduced, suggesting recovery to a poised state where HEXIM1 is sequestered by P-TEFb. In agreement with our hypothesis that P-TEFb release of RNAP2 pausing leads to the dampened response to a second stimulation during the transcriptional refractory period, the presence of a P-TEFb inhibitor during the first stimulation prevents the suppression of the transcriptional response to a second KCl stimulus. Our ongoing work will examine if transcription initiation also impacts IEG induction, and test if modulating elongation influences memory-associated diseases. Collectively, our findings suggest HEXIM1 is essential for priming inducible genes for rapid activation by P-TEFb in response to stimuli.

Disclosures: M. Htet: None. **C.S. Estay:** None. **B.E. Powers:** None. **G.A. Kaas:** None. **R.J. Colbran:** None. **C.B. Greer:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.03/A53

Topic: B.05. Synaptic Plasticity

Support: NIH Grant MH122961
NIH Grant NS083085

Title: Imaging localization and local translation of synaptic mRNAs reveals mechanisms of long-term plasticity

Authors: *S. DAS[1], D. HWANG[2], J. A. ROGOW[3], H. MENDEZ-VAZQUEZ[1], R. H. SINGER[4]; [1]Emory Sch. of Med., Atlanta, GA; [2]Cell Biol., Albert Einstein Col. of Med., Bronx, NY; [3]Neurosci., Albert Einstein Col. of Med., Bronx, NY; [4]Albert Einstein Col. of Med., Bronx, NY

Abstract: Spatio-temporal control of gene expression in a neuronal network is essential for activity-dependent modifications of synapses (synaptic plasticity) and memory formation. Owing to the highly polarized morphology of the neurons, one way of achieving precise control of protein levels is by localizing mRNAs to synapses and locally translating them in response to stimulation to supply new proteins to the remodeled or “plastic” spine. The synapse localized transcriptome consists of thousands of mRNAs, however, the dynamics of individual mRNAs in response to stimulation and their regulation remains less explored. We address these questions by high-resolution imaging of endogenous mRNAs and proteins in living neurons. To this end, we generated knock-in mouse where endogenous *Arc*, *β -actin* and *CamK2a* genes are tagged in their 3'UTR with orthologous bacteriophage-derived stem loops that bind to different fluorescent coat proteins. While constitutive, long-lived *β* -actin mRNAs persisted in the dendrites and undergo multiple rounds of translation, inducible Arc transcripts with short half-lives displayed transient localization with rapid assembly of a translation hotspot. Surprisingly, *CamK2a* mRNAs behaved differently from the other two mRNAs with unique localization inside the dendritic spines. Our results highlight distinct regulatory pathways governing the transport, localization, and translation of these activity-regulated mRNAs to ensure proper synapse functions and facilitate long-term synaptic plasticity.

Disclosures: S. Das: None. **D. Hwang:** None. **J.A. Rogow:** None. **H. Mendez-Vazquez:** None. **R.H. Singer:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.04/A54

Topic: B.05. Synaptic Plasticity

Support: SBIR Grant R44MH119989

Title: Npas4 and cFos Measurement for Rich Brain-Wide Snapshots of Neuronal Activity

Authors: *D. WHEELER[1,2], N. GUANZON[3], Y. GALLEGOS[4], C. REDD[3], E. BLAES[4], M. PETERS[5], L. COUTELLIER[6], R. AZEVEDO[7,4], S. P. GANDHI[8,4];
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Abstract: Providing access to the intricate anatomy of the whole intact brain, tissue clearing offers neuroscientists unbiased and complete views of brain anatomy and function. Translucence Biosystems is developing an ecosystem of tools to help enable a dimensional shift from 2D to 3D histology. Using iDISCO-based tissue clearing methods, a ZEISS Lightsheet Z.1 microscope with our Mesoscale Imaging System, AI-powered whole-brain object segmentation with our BrainQuant3D/3TK software and new statistical methods for anatomics, our pipeline produces regionalized read-outs of cellular patterns across 100's of brain areas. The immediate-early gene (IEG) product, cFos, has been used for decades to monitor changes in neuronal activity. The expression of cFos is driven by Ca^{2+}-signaling downstream of neuronal activity, however, cFos is also driven by cAMP elevations and signaling pathways engaged by neurotrophins or other paracrine factors. In contrast, expression of the IEG product Npas4 is neuron-specific and tightly tuned to Ca^{2+}-dependent signaling pathways. We developed a recombinant rabbit monoclonal anti-Npas4 antibody that works well in a large number of methods and is made available to researchers through Activity Signaling (Npas4.com). Importantly, in iDISCO experiments on Npas4 KO mice, Npas4 immunoreactivity is lost and our AI-powered cell-segmentation tools have a low false-positive rate. Unlike cFos, which is expressed in a large number of neurons throughout the brain in home-cage mice, we find almost no expression of Npas4. Pharmacological stimuli can up-regulate or down-regulate cFos, but due to floor effects only increase Npas4 expression. Typically, pharmacological and behavioral stimuli (e.g. novel environment exposure), induce the expression of both Npas4 and cFos, but Npas4 induction is modest, with protein detected in ~10% as many neurons as cFos. This relatively weak signal is not related to staining sensitivity or poor expression of Npas4 in response to neuronal activity since seizure induction with kainic acid results in robust Npas4 expression in as many or more neurons than cFos. Together, these data demonstrate that cFos and Npas4 have distinct responses to behavioral and pharmacological stimuli and that co-staining of both Npas4 and cFos reveals distinct, but overlapping populations of neurons. To disseminate this technology, the BRAIN Initiative funded the development of our iDISCO-based Neuronal Activity kits, which contain both anti-cFos and anti-Npas4 antibodies, as well as our cloud-based, AI-powered quantification software, to allow researchers to generate rich brain-wide snapshots of neuronal activity.

Disclosures: D. Wheeler: A. Employment/Salary (full or part-time):; Translucence Biosystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc. **N. Guanzon:** A. Employment/Salary (full or part-time):; Translucence Biosystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc. **Y. Gallegos:** A. Employment/Salary (full or part-time):; Translucence Biosystems, Inc.. E. Ownership Interest

(stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc. **C. Redd:** A. Employment/Salary (full or part-time):; Translucence Biosystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc. **E. Blaes:** A. Employment/Salary (full or part-time):; Translucence Biosystems, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc.. **M. Peters:** None. **L. Coutellier:** None. **R. Azevedo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc. **S.P. Gandhi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems, Inc..

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.05/A55

Topic: B.05. Synaptic Plasticity

Support: NIH/NINDS Grant R01-NS112492 (to T.T.)

Title: Mbnl1, an RNA splicing factor, associates with the arc capsid in an activity-dependent manner

Authors: *M. ZINTER[1], C. XIAO[3], P. M'ANGALE[5], R. ZHAO-SHEA[4], T. G. FREELS[6], A. R. TAPPER[2], T. THOMSON[7];
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Abstract: The *Drosophila* activity-regulated cytoskeleton-associated protein (dArc1) forms a viral-like capsid, encapsulates is own transcript and transfers across the synapse. This transfer has been demonstrated to promote synaptic maturation at the *Drosophila* neuromuscular junction and shows conservation to the mammalian neural synapse through the dArc1 mammalian ortholog, (Arc). However, a long-standing question is whether dArc1/Arc is capable of transferring transcripts other than its own. Recently, we established that dArc1 can interact with numerous transcripts in *Drosophila* including the transcript of the RNA splicing factor muscleblind (Mbl). Here, we demonstrate this interaction is conserved to Arc and the mammalian Mbl ortholog, Muscleblind Like Splicing Regulator 1 (Mbnl1). In mouse neuro2a (N2A) cells, immunoprecipitation of the Arc capsid enriches for both *Arc* and *Mbnl1* transcripts. Upon neuronal-like differentiation of N2A cells, the ability of Arc to bind its own transcript and

Mbnl1 is abolished while potassium stimulation of these cells restores interaction of Arc with both transcripts. These data indicate Arc association with *Mbnl1* mRNA may be an activity-dependent process. Furthermore, we demonstrate that both *Arc* and *Mbnl1* RNA can be detected in extracellular vesicles (EVs) derived from N2A cells and that potassium stimulation of differentiated N2A cells alters the ratio of *Arc* to *Mbnl1* transcripts in EVs. We then lysed EVs and nuclease digested intraluminal nucleic acid and established that *Mbnl1* is riding on the Arc capsid surface as opposed to direct encapsulation, elucidating a novel method for vesicular transfer of RNA. Taken together, our data suggest that the Arc capsid interacts with *Mbnl1* RNA in an activity-dependent manner at the capsid surface and this interaction may facilitate transsynaptic transfer of *Mbnl1* RNA through EVs.

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Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

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Program #/Poster #: PSTR102.06/A56

Topic: B.05. Synaptic Plasticity

Support: 2021 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Mapping the colocalization of dendritic RNA cargoes in the hippocampus

Authors: R. TARANNUM, G. MUN, S. A. SWANGER, *S. FARRIS;
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Abstract: Neurons localize thousands of RNAs to dendrites, in part, to support activity-induced rapid remodeling of synapses. For transport, RNAs assemble into multivalent, membraneless condensates containing RNA-binding proteins and other RNAs, collectively termed ribonucleoprotein particles (RNPs). Composition of RNPs is thought to dictate when, where, and how a given RNA is translated, yet how they are packaged for delivery to synapses remains elusive. Dysregulated RNA localization and local translation is the cause of fragile x syndrome, a common cause of inherited autism. Therefore, uncovering the molecular composition of RNPs and the mechanisms governing RNP transport to synapses is crucial for our understanding of synapse function in health and disease. Imaging limitations have restricted visualization to three RNAs at once, making it technically challenging to map RNP composition in situ. To overcome this obstacle, we used highly multiplexed in situ hybridization and iterative imaging to visualize a dozen dendritic RNAs in the mouse hippocampus. We measured colocalization patterns as a proxy for RNA association across twelve putative targets of FMRP, the RNA binding protein lost in fragile x syndrome. Given that FMRP-bound dendritic RNAs encode proteins with diverse functions, we hypothesized that FMRP target RNAs co-assemble into distinct heteromeric RNPs

based on encoded protein function and/or dendritic destination. First, we found that dendritically localized RNPs show heterogeneous size distributions that vary both within and across RNA targets. We propose that these size differences may reflect distinct RNP populations with varying amounts of RNA transcripts and/or RNA species. Second, hierarchical clustering of the pairwise colocalization patterns revealed that for every RNA tested, regardless of its abundance, there was more colocalization with highly abundant RNAs (Camk2a, Ddn) than with lower abundant RNAs (Pum2, Ppfia3). This effect remained after correcting for the degree of colocalization expected by chance. However, there was no obvious relationship between encoded protein function or destination and colocalization pattern. Lastly, we consistently found ~90% of each RNP contained at least two or more RNA species, suggesting that RNAs are unlikely to be singly transported. Taken together, this study provides evidence for heterogeneous RNPs containing multiple types of transcripts in the intact mouse brain and suggests that densely localized transcripts may function as hubs for RNA co-assembly and a potential organizational driver for RNA localization to synapses.

Disclosures: R. Tarannum: None. **G. Mun:** None. **S.A. Swanger:** None. **S. Farris:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

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Program #/Poster #: PSTR102.07/A57

Topic: B.05. Synaptic Plasticity

Support: NIH T32NS061847
NIH Grant R01NS105742
NASEM Predoctoral Ford Fellowship
ARCS Foundation Scholarship

Title: Astrocyte experience-dependent transcriptomic response and contribution to synaptic plasticity in the adult mouse visual cortex

Authors: *M. CONTRERAS[1,2], A. AVALOS[2], I. SMITH[2], L. LABARTA BAJO[1], N. J. ALLEN[1];
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Abstract: Synaptic plasticity is age dependent. Early in life during the critical period, plasticity is heightened and once the circuitry matures, plasticity is restricted in the adult brain. Previous studies suggest synaptic plasticity involves a dynamic interplay between neurons and glial cells. Astrocytes are glial cells involved in the regulation of neuronal synaptic formation, maturation, and plasticity, and exhibit age-dependent transcriptional changes. How astrocytes alter their transcriptome in response to experience-dependent neuronal activity, and if this plays a role in regulating synapse stability, i.e., decreased plasticity in the adult brain, remains unexplored. To investigate astrocyte experience-dependent transcriptomic responses, we performed single nuclei

RNA sequencing of adult visual cortex astrocytes. Following 48 hours of darkness, we exposed 4-month-old mice to 0 or 4 hours of light to stimulate the visual pathway, dissected the visual cortex, specifically enriched for astrocyte nuclei by fluorescence activated cell sorting, and performed single nucleus RNA sequencing. We successfully isolated 59020 astrocyte nuclei from four biological samples, each consisting of adult visual cortices pooled from two mice. We identified 204 upregulated genes and 128 downregulated genes when comparing visually stimulated astrocytes versus non-stimulated astrocytes. To ask which gene programs are enriched by visual stimulation, we performed gene ontology analysis and identified experience-dependent neuronal activity upregulates programs related to synapse organization, synapse structure and activity, and GABAergic synaptic transmission. These results suggest an astrocyte cell-state change that allows rapid response and adaptation. Our results support the hypothesis that astrocytes respond to experience-dependent neuronal activity with transcriptional changes that may contribute to synapse stabilization in the adult brain, and experiments are ongoing to test this hypothesis by manipulating candidate factors in astrocytes. Plasticity alterations have been shown to contribute to neurodevelopmental and neuropsychiatric disorders, and our findings highlight the importance of considering the dynamic interactions between different cell types in the brain when hypothesizing origin and treatment of plasticity-related disorders.

Disclosures: M. Contreras: None. **A. Avalos:** None. **I. Smith:** None. **L. Labarta Bajo:** None. **N.J. Allen:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.08/A58

Topic: B.05. Synaptic Plasticity

Support: Graduate School of Health, Aarhus University
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PROMEMO – Center for Proteins in Memory, a Center of Excellence funded by the Danish National Research Foundation (DNRF133)

Title: Cross-species analysis of novelty-induced memory consolidation reveals increased agap3 transcription

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Abstract: Throughout the day, most of our experiences are automatically encoded as memories in the hippocampus (HPC), and many of these memories fade away and are quickly forgotten. However, the retention of these memories is facilitated when novel or salient experiences occur within 1-2 hours before or after memory encoding. The effects of novelty on cellular or initial memory consolidation have been found to depend on the activation of the locus coeruleus (LC) that leads to dopaminergic signaling in the HPC. Through dopamine D1/D5 receptor activation, novel experiences induce the expression of activity-dependent genes believed to be necessary for initial memory consolidation. Although several genes have been identified as potential candidates, our current understanding is insufficient to fully explain the mechanisms of initial memory consolidation, necessitating the identification of additional candidates. In this study, we established and validated a contextual novelty exploration paradigm in rats that enhances memory persistence in an object location task. We then conducted a cross-species study using this paradigm to induce transcriptional changes in the dorsal HPC of mice and rats. Multiplex mRNA quantification was performed to identify affected genes. Additionally, we assessed the impact of the dopamine D1/D5 receptor antagonist SCH 23390—which inhibits the beneficial effect of novelty on memory persistence—on contextual novelty-induced transcription in rats. We found that genes significantly affected by contextual novelty varied between the two species, with 9 genes upregulated in mice and 3 genes in rats. Comparison across species revealed that ArfGAP with a GTPase domain, an ankyrin repeat and PH domain 3 (Agap3) was the only gene upregulated in both, suggesting a potentially conserved role for AGAP3. AGAP3 is known to regulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor trafficking in the synapse, suggesting that increased transcription of *Agap3* may be involved in maintaining functional plasticity. While we identified several genes affected by contextual novelty exploration, we were unable to fully reverse these changes using SCH 23390 in rats. AGAP3 was identified as a candidate with a potential key role in novelty-induced memory consolidation. Further research into the specific function of AGAP3 during novelty-induced memory consolidation could lead to a better understanding of this process and guide future research.

Disclosures: K. Højgaard: None. **T. Takeuchi:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.09/A59

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01AG070193

Title: Eif4b regulates local activity-dependent protein synthesis and synaptic plasticity in human neurons

Authors: *D. LOKITIYAKUL[1], G. KAUWE[2], I. L. WONG[3], K. PAREJA-NAVARRO[4], T. E. TRACY[2];
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Abstract: Long-term potentiation (LTP), a form of synaptic plasticity linked to the formation of new memories, is defined as the persistent strengthening of synaptic connections in response to neuronal activity. Protein synthesis is required for the expression of LTP at synapses, and neuronal activity regulates the translation of specific mRNAs in dendrites. The activity-dependent mechanisms that regulate translation initiation in dendrites could impact the expression of LTP. Eukaryotic translation initiation factor 4B (eIF4B) is an RNA binding protein that facilitates the recruitment of the preinitiation complex containing eIF3 to mRNA, promoting the initiation of translation. The function of eIF4B has been primarily characterized in non-neuronal cells, but the role of eIF4B in translation initiation in neurons in not well understood. In human induced pluripotent stem cell (iPSC)-derived neurons, immunostaining revealed eIF4B co-localized with other eIF4 complex proteins in dendrites and at synapses. To study the role of eIF4B in neurons, we generated a lentivirus for expression of a short hairpin (shRNA) to knockdown eIF4B in human iPSC-derived neurons. Virus treated neurons were cultured in vitro for 6-8 weeks before experiments. To test the role of eIF4B in translation initiation during LTP expression, neurons were treated with a chemical LTP induction method followed by labeling of newly synthesized proteins with puromycin. Control human iPSC-derived neurons exhibited increased puromycin labeling in dendrites after cLTP induction compared to unstimulated neurons, indicating enhanced protein synthesis in dendrites during LTP expression. This enhancement of protein synthesis during LTP was blocked in human iPSC-derived neurons with eIF4B knockdown, suggesting that eIF4B is required for activity-dependent translation in dendrites. The knockdown of eIF4B also blocked the recruitment of postsynaptic AMPA receptors during LTP expression in human iPSC-derived neurons, supporting that eIF4B is required for the expression of LTP. Overall, our findings suggest that eIF4B could be an activity-dependent molecular switch that turns on protein synthesis in dendrites for the expression of LTP at synapses.

Disclosures: D. Lokitiyakul: None. **G. Kauwe:** None. **I.L. Wong:** None. **K. Pareja-Navarro:** None. **T.E. Tracy:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

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Program #/Poster #: PSTR102.10/A60

Topic: B.05. Synaptic Plasticity

Support: HHMI
NIMH R01-MH116900

NICHD R01-HD097088
NIDA R01-DA056595

Title: Profiling Neural Protein Dopaminylation with Age and in Parkinson's disease

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Abstract: Monoamines, such as dopamine, serotonin, and histamine, were historically believed to function exclusively via membrane bound receptors and play critical roles in neuronal networks that regulate cognition, reward, and motor learning, among other processes. Dopaminergic neuron firing and dopamine levels decrease with normal aging in the substantia nigra, and drastic declines in dopamine signaling have been linked to a range of age-related disorders, including Parkinson's Disease (PD). More recently, monoamines have been shown by our lab to serve as chemical donors for a novel class of post-translational modification, termed monoaminylation - i.e. the covalent modification of histones and other proteins by monoamine neurotransmitters. Here, we utilize a novel chemical tagging approach to profile alterations to the protein "dopaminylome" with age and in PD across various brain regions using mouse and postmortem human brain tissues. From postmortem human brain samples, we have identified a global loss of dopaminylation of multiple proteins in the human prefrontal cortex of individuals with PD, consistent with PD associated loss of dopamine tone and the death of dopaminergic neurons. Furthermore, we have identified reductions in neural Histone 3 glutamine 5 dopaminylation (H3Q5dop), as well as the associated combinatorial mark H3K4me3Q5dop, without global reductions in H3K4me3 within the substantia nigra of subjects with PD. Interestingly, enhancing H3K4me3 transcription is known to have neuroprotective effects in PD rodent models, and the deposition of H3Q5dop stabilizes and potentiates H3K4me3 to increase permissive transcription. Thus, ongoing experiments aim to implement a dominant negative mouse model to identify the impact of H3Q5dop reductions on the epigenomic landscape and motor learning behavior.

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Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

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Program #/Poster #: PSTR102.11/A61

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R37NS115439
NIH Grant 1K08NS119797-01A1
Harold Amos Medical Faculty Development Program

Title: Early life seizures induce persistent transcriptomic dysregulation in specific neuronal subpopulations

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Abstract: Early-life seizures (ELSs) can cause permanent cognitive deficits and network hyperexcitability. Using mice with targeted recombination of activated populations (TRAP) we genetically labeled neurons activated by kainate-induced ELSs in immature mice (P10). The ELS-TRAPed neurons, marked with tdTomato (tdT) as a reporter gene under the immediate early gene cFos promoter, were highly enriched in the hippocampal CA1 region. These tdT+ neurons showed persistent changes, including increased activation of GluA2 lacking AMPA subtype receptors, occluded long-term potentiation and depression, and remained preferentially susceptible to reactivation by later life seizures in adulthood (P60) (PMID: 38227384). Given the phenotypic differences of these neurons, we aimed to identify unique transcriptomic alterations in activated tdT+ compared to surrounding tdT- CA1 pyramidal neurons. Following ELS-TRAP at P10, we used fluorescence-activated cell sorting (FACS) to separate tdT+ and tdT- nuclei from miscrodissected hippocampal tissue at P30, followed by single-nucleus RNA-sequencing (snRNA-seq) analysis. *Seurat* and *enrichR* were used to identify cell types and analyze differential gene expression. Gene ontology analysis revealed prominent dysregulation in several pathways related to chemical synaptic transmission in glutamatergic neurons. Genes that were most significantly dysregulated included an increase in *Gria1* and *Grin2b* with a related decrease in *Grin2d* and *Grid2*. By contrast, GABAergic neurons and non-neuronal cells demonstrated more prominent changes in genes involved in mRNA processing. These findings show that enduring transcriptomic modifications occur in a subpopulation of ELS-activated neurons, compared to the surrounding neurons. Consistent with the persistent hyperexcitability and synaptic dysplasticity we have previously reported, modifications were most prominent in glutamate receptor subunits. Determining the time course of such changes following ELS provides a basis for future studies to examine potential targetable pathways that may yield novel clinically relevant therapies to prevent long-lasting cognitive deficits and epilepsy following ELS.

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Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

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Program #/Poster #: PSTR102.12/A62

Topic: B.05. Synaptic Plasticity

Support: 2R01MH116900-06A1
5F32MH126534-02

Title: MLL5 preferentially binds histone serotonylation (H3K4me3Q5ser), regulating chromatin dynamics and orchestrating crucial transcriptional programs during neurodevelopment

Authors: *B. H. WEEKLEY[1], J. CHAN[1], I. S. MAZE[1,2];
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Abstract: Monoamine neurotransmitters play a key regulatory role during neurodevelopment. In particular, dysregulation of serotonin (5-HT) has been implicated in the pathophysiology of neurodevelopmental disorders, including autism spectrum disorders (ASD), yet the molecular mechanisms underlying 5-HT's contribution to neurodevelopment remains unclear. Our group recently identified covalent monoaminylation of histones in brain (specifically histone H3 at glutamine 5 - H3Q5ser). Deposition of 5-HT at this site stabilizes neighboring H3K4me3, resulting in the combinatorial H3K4me3Q5ser, recruiting regulatory machinery to increase permissive transcription. During neurodevelopment in mice, we found global shifts in H3K4me3 and H3K4me3Q5ser enrichment patterns in forebrain, noting alterations in the appearance of broad domains (2.5-35 kb) vs. typical narrow domains (0.5-2.5 kb). Broad H3K4me3 domains have been shown to be enriched at gene loci involved in synaptic signaling in mice and humans, suggesting conservation of neuron-specific function in brain. A screen of known histone "reader" domains identified the plant homeodomain (PHD) finger of *KMT2E* (MLL5) as binding stronger to H3K4me3Q5ser vs. H3K4me3 alone, suggesting it may play a role during neurodevelopment. Isothermal titration calorimetry revealed a ~5-fold increase in binding, which we replicated using peptide immunoprecipitations (IPs) of MLL5. While MLL5 has been shown to be catalytically inactive, studies highlight its crucial role in neurodevelopment, with mutations in *KMT2E* found in children with symptoms related to ASD, developmental delay, epilepsy, and macrocephaly. To investigate its role in neurodevelopment, we generated *Kmt2e* $^{-/+}$ & $^{-/-}$ mice, and RNA-seq revealed robust gene expression changes in KO neurons. Behavioral assays revealed altered anxiety-like behaviors, deficits in motor coordination, altered sensitivity to sensory stimuli and increased vulnerability to seizures in KO animals. To date, there are no defined roles of MLL5 in chromatin regulation. To investigate this further, we knocked-in a FLAG tag on *KMT2E* in human cells and performed FLAG IPs coupled to mass spectrometry to identify novel binding partners. The results identified all core components of the Nuclear co-receptor (NCoR)/Histone Deacetylase 3 (HDAC 3) complex as strong interactors of MLL5. Ongoing experiments aim to characterize interactions between MLL5 and the NCoR/HDAC3 complex, MLL5's regulation of H3K4me3 and H3K4me3Q5ser broad domains during neurodevelopment in mice, and its control over resulting transcriptional patterns that may contribute to synaptic connectivity and behavior.

Disclosures: B.H. Weekley: None. **J. Chan:** None. **I.S. Maze:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

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Program #/Poster #: PSTR102.13/A63

Topic: B.05. Synaptic Plasticity

Title: Identification of the quinone reductase NQO2 as a novel reader of histone H3 serotonylation that contributes to permissive neural gene expression

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Abstract: Monoaminergic neurotransmission in the central nervous system (CNS) plays a critical role in brain development and function, with alterations in monoamine production/signaling implicated in the development and treatment of many neurological disorders, including substance use disorders, mood syndromes and neurodegeneration. Serotonin - as well as other monoamines - have previously been shown to form covalent bonds with certain cytoplasmic proteins, catalyzed by the Transglutaminase 2 enzyme, and our group recently identified histone proteins as robust substrates for monoaminylation in brain (specifically histone H3 at position glutamine 5 - H3Q5ser). Our data indicate that histone serotonylation acts to alter the binding of histone/DNA modification interacting proteins and plays direct roles in neural transcription, particularly during periods of increased cellular activity. Furthermore, we have uncovered pathophysiological associations between altered levels of H3 monoaminylations and behavioral deficits observed in rodent models of disease. Importantly, however, the field has yet to uncover H3Q5 monoaminylation specific 'readers' that may contribute to transcriptional plasticity in brain. As such, we recently profiled H3Q5ser interacting proteins in cellular nuclear extracts via immunoprecipitations using biotinylated chemically modified H3 peptides, followed by LC-MS/MS mass spectrometric identification. In doing so, we found the N-ribosyldihydronicotinamide: quinone reductase 2 (NQO2) to be robustly increased in its binding to H3 in the presence of Q5ser, an interaction that was subsequently validated using both biophysical and X-ray crystallography-based approaches. In addition, we have identified two mutations within NQO2 (NQO2-I129EI129R and NQO2-I129R195E), which can abolish NQO2's H3Q5ser binding without impacting the enzyme's endogenous quinone reductase activities. Now, employing a wide variety of biochemical, genome-wide and protein engineering strategies, we are mechanistically assessing functional roles for NQO2-H3Q5ser interactions in the regulation of permissive gene expression in neurons. In sum, our work has identified a previously uncharacterized and *bona fide* 'reader' of novel H3Q5ser, which likely contributes significantly to H3 serotonylation mediated gene expression in the CNS.

Disclosures: M. Chen: None. **I.S. Maze:** None. **K. Rosenblum:** None.

Poster

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Program #/Poster #: PSTR102.14/A64

Topic: B.05. Synaptic Plasticity

Support: NIH R01 MH116900-04
HHMI Ian Maze

Title: Dissecting regional and cell-type specific roles for Histone H3 serotonylation in stress-mediated dysregulation of neural transcription

Authors: *G. DI SALVO[1,2], A. AL-KACHAK[3], E. BRINDLEY[4], J. CHAN[4], B. WEEKLEY[6], J. BENETATOS[7], L. TIAN[8], Y. HUA[9], L. LOOGER[10], I. S. MAZE[5,11];
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Abstract: We recently demonstrated that serotonin (5-HT), in addition to its canonical role as a neuromodulator, can serve as donor for the establishment of covalent modifications on Histone H3 at position glutamine 5 (Q5), often found in combination with adjacent lysine 4 trimethylation (H3K4me3Q5ser) to promote permissive transcription in neural cells. More recently, we found that within dorsal raphe nucleus (DRN) - the primary source of serotonergic projections in brain - chronic exposures to social stress impact H3K4me3Q5ser mediated transcriptional states, contributing to the persistence of stress vulnerability. Moreover, we found that chronic antidepressant (selective serotonin reuptake inhibitor/SSRI) treatments reverse stress susceptibility and rescue aberrant stress-induced H3K4me3Q5ser dynamics in DRN, effects that can be phenocopied by viral mediated attenuation of H3K4me3Q5ser dynamics in response to chronic social stress. While such studies indicated that stress-induced alterations in H3K4me3Q5ser in DRN are implicated in the precipitation of depressive-like phenotypes, little remains known regarding cell-type specific contributions of H3 serotonylation to stress-induced phenotypes in DRN or its potential roles in serotonergic projection regions. Thus, we expanded our investigations of H3K4me3Q5ser (dys)regulation in response to chronic stress -/+ SSRI treatments to the medial prefrontal cortex (mPFC), a DRN projection region implicated in emotional responsivity. Next, given that H3K4me3Q5ser has been found to be expressed across both neuronal and glial cell of DRN and mPFC, we are dissecting H3K4me3Q5ser dynamics in response to chronic social stress at single-nucleus (sn) resolution across both regions using snCUT&Tag. By integrating this approach with snRNASeq, we aim to delineate the cell type-specific contributions of H3 serotonylation to stress vulnerability and resilience in both DRN and mPFC. Moreover, preliminary data indicate that H3K4me3Q5ser levels are largely dependent on intracellular 5-HT concentrations, yet the temporal dynamics through which 5-HT reaches nuclear compartments and neuronal chromatin remain unclear. To uncover this aspect, we are employing intracellular (cytoplasmic, nuclear, chromatin) iSeroSnFR sensors, which allow for real-time monitoring of 5-HT influx and localization across various cell compartments and specific cell-types. Thus, future studies will aim to utilize iSeroSnFR sensors in live mouse models to capture 5-HT dynamics in response to chronic stress -/+ SSRIs, which promises to aid in our understanding of 5-HT's involvement in stress-induced depressive-like phenotypes.

Disclosures: G. Di Salvo: None. **A. Al-Kachak:** None. **E. Brindley:** None. **J. Chan:** None. **B. Weekley:** None. **J. Benetatos:** None. **L. Tian:** None. **Y. Hua:** None. **L. Looger:** None. **I.S. Maze:** None.

Poster

PSTR102: Transcription and Translation in Plasticity

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.15/

Topic: B.05. Synaptic Plasticity

Support: NIH Grant AG068423
Alzheimer's Association Research Grant 1026776
NARSAD Young Investigator Grant

Title: Tools to study functions of local protein synthesis in neurons

Authors: *J. PARK;
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Abstract: Protein homeostasis relies on precise control that orchestrates the location, abundance, and conformational status of more than 25,000 proteins in humans. Protein synthesis is critical for synaptic plasticity and memory. Evidence indicates that mRNA transcripts, ribosomes, and other translational factors are distributed in various cytoplasmic compartments of neurons, implying the functional roles of local protein synthesis across neuronal compartments. However, the diffuse nature of conventional, drug-based protein synthesis inhibitors (PSIs) makes it challenging to specifically control local protein synthesis, limiting the functional studies. To overcome this challenge, we employed a genetically encodable PSI, modified it to target dendritic spines or axonal terminals, and validated them as compartment-targeted PSIs that can selectively inhibit dendritic or axonal translation. Using these tools, we found that selective inhibition of hippocampal dendritic translation prevents synaptic plasticity and memory formation in mice. Moreover, we found that post-conditioning inhibition of dendritic translation in hippocampal engram neurons leads to a significant reduction of pre-formed memory in mice. We also found that selective inhibition of hippocampal axonal translation prevents maintaining intact axonal projections in vivo. Altogether, the data acquired with these compartment-targeted PSIs indicate the critical functional roles of local protein synthesis in neuronal structure, plasticity, and functions.

Disclosures: J. Park: None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.01/A65

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Title: Mapping spatial organization of functional inputs

Authors: *V. REGIO[1,2], D. CUPOLILLO[1], A. BARBERIS[1];
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Abstract: The formation of memories in response to aversive or rewarding stimuli is crucial in guiding avoidance or approach behaviors. Scattered, projection-defined neuronal populations within the basolateral amygdala (BLA) selectively activate during encoding and retrieval of memories associated with either positive or negative valence. Interestingly, BLA neurons projecting to the CA1 area of ventral hippocampus (vCA1) respond to both positive or negative predicting cues with no marked bias, suggesting that, within the whole responding population, two distinct subnetworks relay opposite information to vCA1. However, the mechanism by which vCA1 pyramidal neurons discern between positive and negative-related information remains unclear. The valence information might stay segregated within two distinct neuronal populations in vCA1, or it might also converge onto the same vCA1 neurons, which have the capability to specifically encode negative or positive valence. We suggest that valence-activated BLA neurons contact vCA1 dendrites in a precise spatial organization, generating valence-related spiking patterns in the postsynaptic neuron. To validate this hypothesis, we aim to create a map of the spatial location of functional synaptic inputs onto vCA1 pyramidal neurons by employing a combination of single-spine calcium imaging, electrophysiology, and optogenetic. By exploiting this approach, we demonstrated the unique distribution of BLA inputs onto the dendrites of vCA1 pyramidal neurons.

Disclosures: V. Regio: None. **D. Cupolillo:** None. **A. Barberis:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.02/A66

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: MathWorks Science Fellowship

Title: Burst firing in visual cortex of awake mice does not depend on layer 1 apical input, and encodes both bottom-up and top-down information

Authors: *V. D. TANG[1], M. HALGREN[2], S. GAO[3], M. T. HARNETT[3];
[1]MIT Grad. Brain and Cognitive Sci., Cambridge, MA; [2]MIT, Cambridge, MA; [3]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: High frequency burst firing occurs throughout mammalian cortex in vivo, yet both the underlying mechanisms and functional role of bursts are unclear. Burst firing in brain slices is strongly modulated by the activity of apical dendrites, which branch extensively in layer 1 (L1) and receive long-range inputs from higher-order cortical and thalamic areas. These properties suggest a powerful subcellular substrate by which single pyramidal neurons could multiplex bottom-up and top-down information via L1-independent tonic spikes and L1-dependent bursts, respectively, and have provided a basis for emerging theoretical models of cortical computation and learning. However, our understanding of burst firing and subcellular processing remains critically limited by a lack of evidence in awake animals. It is unclear whether burst firing a) is preferentially recruited by bottom-up versus top-down inputs, and b) requires apical dendritic engagement. To answer these questions, we performed high-density extracellular recordings in primary visual cortex of awake mice while presenting a battery of classical (bottom-up) and extra-classical (top-down) visual stimuli. We report ubiquitous high frequency bursts, with consecutive action potentials exhibiting decrementing waveform amplitudes consistent with dendritic plateau potentials. However, contrary to expectation, bursts exhibited extremely short response latencies, and were recruited in the initial bottom-up response to visual stimuli. Furthermore, bursting was strongly driven by both classical and extra-classical visual stimuli, inconsistent with a selective role for cortical bursting in representing top-down visual information. We then tested the contribution(s) of apical dendrites to burst firing and extra-classical tuning via two optogenetic manipulations; L5 pyramidal neuron inhibition and NDNF interneuron activation, which respectively enact either blanket or selective apical inhibition. Burst spikes were selectively reduced by targeted L1 inhibition but not blanket inhibition, demonstrating that in vivo burst spiking is modulated by L1 feedback excitation. However, the magnitude of this inhibition was modest, further suggesting that bursting is strongly driven by bottom-up inputs. Apical tuft inhibition did not differentially affect classical vs extra-classical visual responses, indicating that extra-classical tuning does not require top-down inputs to L1. Taken together, these results suggest that burst spiking is robustly generated by multiple subcellular mechanisms in vivo, contradicting theories in which bursting is selectively driven by feedback inputs to L1.

Disclosures: V.D. Tang: None. **M. Halgren:** None. **S. gao:** None. **M.T. Harnett:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.03/A67

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH grant R01MH115832 under the CRCNS program (C.C.C and S.G.)
Research Enhancement Program of the School of Medicine at LSUHSC-NO (S.G.)

Title: Cholinergic modulation increases excitability and facilitates plateau potentials in hippocampal CA1 pyramidal neurons via activation of TRPM4 channels

Authors: C. L. COMBE[1], C. M. UPCHURCH[2], C. C. CANAVIER[2], *S. GASPARINI[1]; [1]Neurosci. Ctr., [2]Cell Biol. and Anat., LSU Hlth. Sci. Ctr. New Orleans, New Orleans, LA

Abstract: The cholinergic system that arises from the basal forebrain has been implicated in cognitive functions including attention and learning and memory; its dysfunction is thought to play a role in cognitive disorders such as Alzheimer's disease and schizophrenia. Hippocampal area CA1 receives cholinergic afferents from the medial septum and diagonal band of Broca; cholinergic tone in the hippocampus is generally high during explorative behavior in a novel environment and is thought to alter network dynamics in a way that allows more efficient encoding of novel stimuli.

Using *in vitro* electrophysiology in hippocampal slices from rats and mice, as well as *in silico* simulations in a multicompartmental model, we examined the effects of cholinergic modulation on hippocampal CA1 pyramidal neurons. We found that the broad-spectrum cholinergic agonist carbachol (CCh, 2 μM) increases excitability of CA1 pyramidal neurons via a depolarizing shift in the steady state I-V curve. Furthermore, we found that CCh facilitates the initiation of dendritic plateau potentials following theta-burst co-activation of excitatory synapses in the perforant path from the entorhinal cortex and Schaffer collaterals from hippocampal area CA3. Similarly, CCh enables the initiation of dendritic plateau potentials during a 300 ms somatic depolarizing current injection. We found that these effects were mediated by the activation of M1 muscarinic receptors, as they could be reversed by the antagonist pirenzepine (1 μM). Cholinergic modulation is known to cause down-regulation of SK and M-type (K_V7) K^+ channels; however, blocking these channels with apamin (100 nM) and XE-991 (10 μM), respectively, did not facilitate dendritic plateau potentials. Moreover, dendritic plateau potentials were abolished by CBA (50 μM), a selective antagonist for TRPM4 channels that mediate the Ca^{2+}-activated nonspecific cation current, I_{CAN}. These data and model simulations suggest that a positive feedback loop between Ca^{2+} entry and TRPM4 activation is responsible for these cholinergic-mediated plateau potentials. Behavioral Timescale Synaptic Plasticity (BTSP), which is hypothesized to mediate place cell formation *in vivo*, requires plateau potentials, thus we speculate that TRPM4 channels may participate in that form of synaptic plasticity as well.

In summary, our synergistic experimental/computational approach has led us to reinterpret the effects of acetylcholine on hippocampal CA1 pyramidal neurons in terms of activation of TRPM4 channels, in addition to down-regulation of SK and M-type (K_V7) K^+ channels.

Disclosures: C.L. Combe: None. **C.M. Upchurch:** None. **C.C. Canavier:** None. **S. Gasparini:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.04/A68

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH R01DC020123

Title: Deciphering decision-making mechanisms: A computational exploration of associative memory in Drosophila

Authors: *M. KHOSHKHOU[1], R. ZIEGLER[3], K. VELLIANGIRI[2], J. JOYCE[2], J. PIELAGE[3], E. NIEBUR[2];
[1]Mind/Brain Inst., [2]Neurosci., Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Biol., Univ. of Kaiserslautern, Kaiserslautern, Germany

Abstract: Learning to associate neutral stimuli with valence information and to retain these associations as memories is crucial for decision-making. To clarify the cellular and circuit mechanisms underpinning associative memory formation in the context of decision-making, we generate a realistic computational model of decision modules within the Drosophila's nervous system. Each module consists of one mushroom body output neuron (MBON) and the synaptic contacts from all its presynaptic Kenyon cells (KCs). We first determine the physiological parameters of each MBON by patch-clamp electrophysiology and collect electron microscopy (EM) data of morphology and synaptic coordinates for each MBON from Hemibrain and FlyWire databases. We incorporate this data into NEURON to generate anatomically and physiologically realistic in silico models of each MBON and its KC inputs. Our results for three independent modules provide evidence that these MBONs are electrotonically compact. We co-activate random sets of KCs to mimic the encoding of an odor by each module and show that synaptic input corresponding to simulated odor input robustly drives spiking behavior of these MBONs. Finally, we modulate the number of co-activated KCs or the strength of KC-to-MBON synapses to examine the effect of different plasticity mechanisms in each memory module, and we show that the amplitude of somatic voltage for these MBONs depends linearly on both the number and strength of active KC-to-MBON synapses. Therefore, sparse innervation by KCs can efficiently control and modulate MBON activity in response to learning with minimal requirements on the specificity of synaptic localization. Additionally, we aim to utilize machine learning techniques to perform all the data pre-processing steps automatically, and we will provide a Python package which helps to conduct the entire analysis with minimal human supervision.

Disclosures: M. Khoshkhou: None. **R. Ziegler:** None. **K. Velliangiri:** None. **J. Joyce:** None. **J. Pielage:** None. **E. Niebur:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.05/A69

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: JST SPRING, Grant Number JPMJSP2110
KAKENHI 22K19360
KAKENHI 22H02721

Title: Spatial processing of excitatory synaptic potentials in dendrites revealed by voltage imaging

Authors: *R. HIGASHI, M. MORITA, S.-Y. KAWAGUCHI;
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Abstract: Neurons receive excitatory synaptic inputs mainly at their dendrites. Synaptic potentials at one point in a dendrite travel through the somatodendritic compartments, where they are spatiotemporally integrated to affect opening of ion channels leading to generation of action potentials. Propagation of synaptic potentials and the resultant integrative property of neurons are essential for their computational ability. However, due to the difficulty of simultaneous patch-clamp detection of membrane potentials at multiple points in a complex dendritic branches, the whole picture of electrical signal processing along dendritic arbors remains elusive. Fluorescent imaging using genetically-encoded voltage indicators (GEVIs), which are proteins that change fluorescence intensity depending on membrane potential, is a useful method to address this problem. Here, we transfected a GEVI, ASAP (St-Pierre et al., *Nat. Neurosci.*, 2014), to cultured hippocampal pyramidal neurons or cerebellar Purkinje cells. Using the fast and high-sensitivity GEVI together with high-speed camera, we were able to quantitatively measure membrane potential changes as small as 1 mV throughout the dendrite. We evoked excitatory postsynaptic potential (EPSP) by photolysis of MNI-caged-L-glutamate by illumination of 405 nanometer laser spot (~ 2 micrometer) on the dendrite, which was monitored as fluorescence change of ASAP. In hippocampal pyramidal neurons, evoked EPSPs showed exponential decrease in the amplitude (length constant >100 micrometer) as traveling toward the soma from the site of glutamate input, becoming almost undetectable at distant arbors. Conversely, in cerebellar Purkinje cells, EPSPs attenuated only in small area around the input site (~ 30 micrometer), and membrane potential change of substantial size (~ 60 % of EPSP size at the glutamate input site) spread over the whole dendritic arborization. For quantitative analysis of these results, we constructed cable theory-based multi-compartment models mimicking the actual geometry of each type of neurons used for voltage imaging. Simulation suggested that the dendritic morphology, such as their thickness and arborization pattern, was the primary determinant of voltage propagation patterns observed in distinct types of cells. In this poster presentation, we will show the computational design of neurons and its strong relationship to their morphological design uncovered by a novel fluorescent imaging technique.

Disclosures: R. Higashi: None. **M. Morita:** None. **S. Kawaguchi:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.06/A70

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Title: Inhibition of ryanodine receptors by calmodulin conrols spatial specificity of calcium transients in old age

Authors: *J. JEDRZEJEWSKA-SZMEK;
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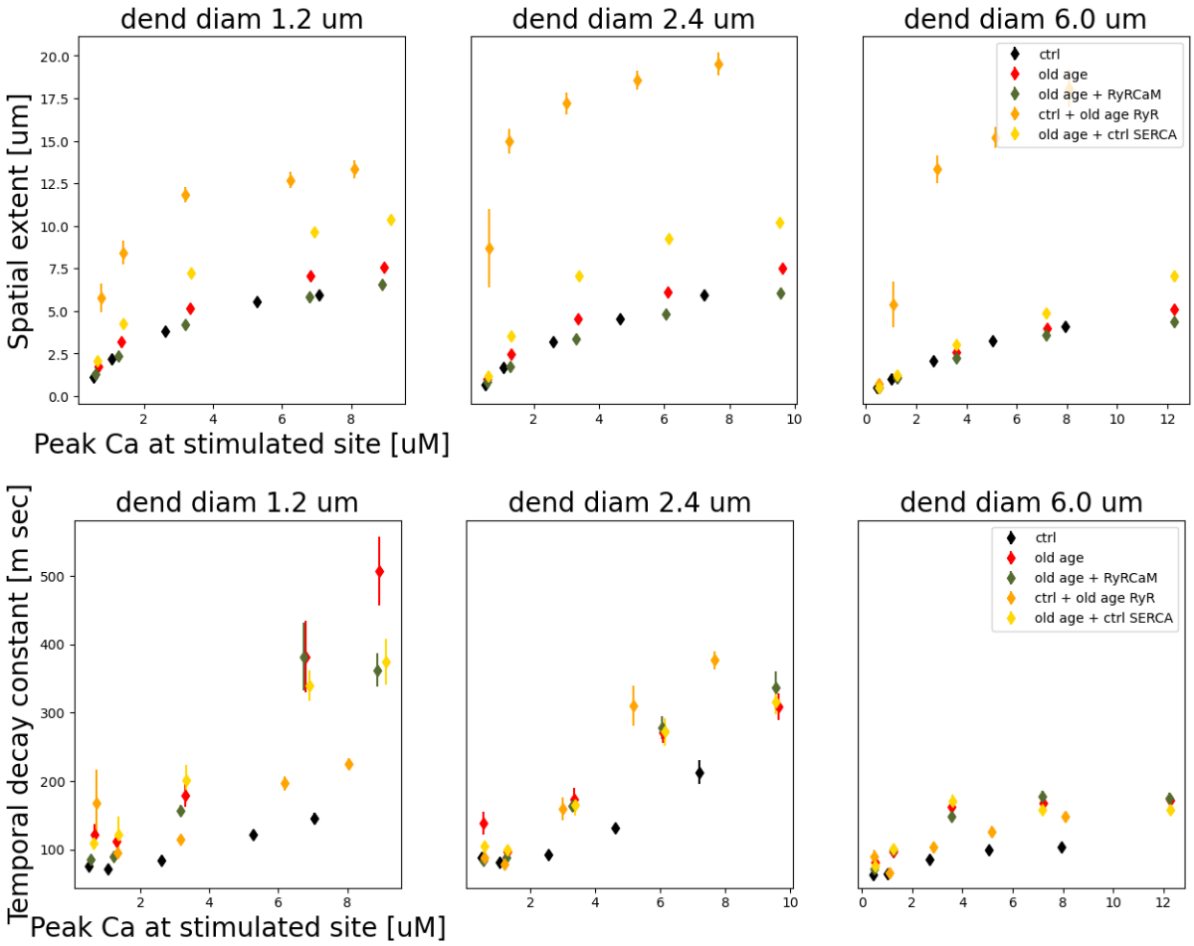
Abstract: Changes in intracellular calcium concentration such as calcium waves regulate cell signaling events in all cells. It has been shown that synaptic activation in pyramidal neurons can elicit propagating calcium waves mediated by calcium release through IP3 receptors from the endoplasmic reticulum (ER). However, much less is known about calcium signals induced by calcium activation of ryanodine receptors (calcium-induced calcium release) in the ER membrane of dendrites. Dendritic branches are often viewed as primary computational units and cognitive decline in aging and neurodegeneration is often accompanied by diminished spatial and stemporal specificity of calcium transients making calcium events a good candidate for the process underlying dendritic computation. Using a spatial stochastic reaction-diffusion model of a CA1 pyramidal thin, medium and thick dendrite we show that ryanodine type 2 receptors (RyR2), which are expressed in dendrites of CA1 pyramidal neurons, can not support synaptically induced calcium wave propagation even when the calmodulin inhibition of RyR2 is relieved. RyR2 activation increases the spatial extent of synaptically evoked calcium transients and introduces a dependence of calcium transient duration on dendritic diameter. The spatial extent of synaptically evoked calcium transients is highest for thin dendrites and lowest for thick dendrites. Furthermore, we show that dis-inhibition of ryanodine type 2 receptors lowers spatial and temporal specificity of calcium transients in the dendrite. Using a model of CA1 pyramidal dendrites in old age we show that spatial and temporal specificity of calcium transients is diminished in old age due to oxidization of calmodulin, which increases spatial spread of calcium by dis-inhibiting RyR2s and prolongs calcium transients by lowering the activity of PMCA pumps. Finally, we propose that experiments utilizing calcium indicator dyes might not show the effect of calmodulin inhibiting RyR2s on spatial specificity of calcium transients.



Disclosures: J. Jedrzejewska-Szmek: None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.07/A71

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant 5R01NS123396

Title: Location-dependent effects of clustered synaptic inputs on a model L5 pyramidal neuron

Authors: *J. SHI[1], D. B. HEADLEY[2];
[1]Ctr. for Mol. and Behavioral Neurosci., Newark, NJ; [2]Rutgers, The State Univ. of New Jersey, Newark, NJ

Abstract: Traditionally, individual neurons were treated as simple passive integrators of synaptic inputs. Recently there has been a growing awareness of their complex integrative abilities, which arise from three properties. First, dendrites contain their own active regenerative spiking events (dendritic spikes), such as NMDA and calcium spikes. Second, synaptic terminals that are correlated in their activities tend to cluster along the dendrites, increasing the chance that a dendritic spike will occur. Third, the same presynaptic axon contacts the dendritic tree at multiple sites, allowing it to interact with other inputs through dendritic spiking. Perhaps crucially, these properties of dendritic integration may interact with the morphology and branching structure of the dendritic tree. Our understanding of this interaction is limited, and much of the work has been performed in the absence of in vivo-like naturalistic synaptic inputs. To address this, we examined integration of correlated synaptic drive using a biophysically detailed layer 5b pyramidal neuron model receiving a realistic number of synapses (excitatory≈16k, inhibitory≈2.7k) driven at a rate consistent with in vivo firing (excitatory = 1, inhibitory = 10 Hz). To simulate coordinated afferent drive, a subset of afferents was driven synchronously (5 ms SD). We systematically varied the number of activated afferents, whether they targeted basal dendrites or the apical tuft, and the branch order (number of forks towards the soma or apical nexus) of targeted dendritic compartments. We then measured the incidence of NMDA spikes, calcium spikes, and somatic action potentials in response. We validated a step-function relationship between the number of activated afferents and induction of an NMDA spike at the level of a single synaptic cluster. Across clusters the relationship between the number of activated afferents and NMDA spikes was more gradual, reflecting cluster specific differences in the number of afferents required to drive an NMDA spike. The threshold for eliciting an NMDA spike was lowest at higher order dendritic branches, which were farthest from the soma. This trend was especially the case for branches in the apical tuft. On the other hand, the threshold for the number of NMDA spikes required to elicit a calcium spike or action potential decreased with branch order from the apical nexus or soma, respectively. These results are consistent with the electrotonic properties of the dendritic tree.Further work is needed to examine how these factors impact the integration of population codes in the dendritic tree.

Disclosures: J. Shi: None. **D.B. Headley:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.08/A72

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NSERC grant 342292-2012
CIHR grant MOP-137072
CIHR grant MOP-142447

Title: Cell-type-specific dendritic integration rules in hippocampal CA1 OLM interneurons

Authors: *M. KANIA[1,2,3], A. TZILIVAKI[4], E. BONONGE[1,5], L. MARTIN[5], V. DULAM[1,5], F. MICHAUD[1], D. TOPOLNIK[1], L. TOPOLNIK[1,5];
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Abstract: Oriens-lacunosum moleculare (OLM) cells, identified as inhibitory interneurons in the hippocampus, play a crucial role in regulating information flow within the CA1 area. They employ inhibitory and disinhibitory circuit motifs to suppress cortical signals to the distal dendrites of CA1 pyramidal cells while facilitating CA3 input. OLM cells receive excitatory synaptic input from CA1 pyramidal neurons and inhibitory inputs from VIP-expressing interneurons. However, the manner in which these inputs are integrated in OLM dendrites to regulate dendritic spike initiation remains largely unexplored. Through a combination of patch-clamp recordings, morphological reconstructions, and single-molecule multiplex RNAScope assays, we have identified three distinct types of OLM interneurons, each possessing unique physiological, morphological, and molecular characteristics. By incorporating this data into biophysically detailed models of OLM cells, along with their excitatory and inhibitory synaptic inputs, we investigated the rules governing dendritic integration in OLMs and the impact of dendritic inhibition from VIP interneurons. Our findings indicate that all types of OLM cells demonstrate supra-linear integration of excitatory inputs, with cell-type-specific nuances. The threshold for generating dendritic action potentials decreased with distance from the soma and dendritic diameter, due to higher input resistance. Additionally, supra-linear dendritic integration was modulated by gradients of both L-type calcium (VGCC-L) and sodium (VGNC) voltage-gated currents, with proximal dendrites influenced by VGCC-L and VGNCs, and distal controlled by VGNCs. Ongoing experiments simulating the connectivity motifs and properties of VIP-to-OLM inputs aim to provide further insights into how dendritic integration in different subtypes of OLM cells is governed by specific subpopulations of VIP cells, shedding light on cell-type-specific integration principles in interneurons and the information selection process within hippocampal microcircuits.

Disclosures: M. Kania: None. **A. Tzilivaki:** None. **E. Bononge:** None. **L. Martin:** None. **V. Dulam:** None. **F. Michaud:** None. **D. Topolnik:** None. **L. Topolnik:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.09/A73

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: R01 NS130917

Title: Confidence and degeneracy in parameter estimation of biophysical neuron models

Authors: *S. NAMAZIFARD[1], A. KHADDAJ[2], M. HEINKENSCHLOSS[3], F. GABBIANI[4];
[1]Baylor Col. of Med., Houston, TX; [3]Computat. Applied Mathematics and Operations Res., [2]Rice Univ., Houston, TX; [4]Baylor Col. Med., Houston, TX

Abstract: A large body of work has been devoted to fitting biophysical models of neurons based on compartmental models and on the Hodgkin-Huxley formalism used to describe their membrane conductances. Yet, little attention has been devoted to characterizing how reliable such parameter estimates are, and how possible degeneracy in model parameters may be identified. To address these questions, we analyzed parameter optimization in simplified passive compartmental models amenable to analytical solutions, as well as numerical optimization of the same models and more realistic single compartment models based on electrophysiological data. Both non-linear programming techniques and multiple shooting were used for numerical parameter optimization. This allowed us to use second order derivative information obtained through automatic or symbolic differentiation for confidence interval estimation and degeneracy analysis. In principle, our methods extend to large-scale, realistic compartmental models of single neurons.

Disclosures: S. Namazifard: None. **A. Khaddaj:** None. **M. Heinkenschloss:** None. **F. Gabbiani:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.10/A74

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: Allen Institute for Neural Dynamics
NIH Grant DP2NS136990
NIH Grant R44MH129023
Chan Zuckerberg Initiative
NIH Grant T32GM136577

Title: Measurement of input-output signals in vivo using high-speed two-photon microscopy

Authors: *M. E. XIE[1], A. NEGREAN[2], L. KINSEY[2], G. JAINDL[3], A. CHARLES[4], K. PODGORSKI[2], K. SVOBODA[2];
[1]Johns Hopkins Univ. / Allen Inst. for Neural Dynamics, Seattle, WA; [2]Allen Inst. for Neural Dynamics, Allen Inst., Seattle, WA; [3]MBF Biosci., Ashburn, VA; [4]Johns Hopkins Univ., Baltimore, MD

Abstract: The neuron is the fundamental information-processing unit of the brain, converting patterns of synaptic inputs into output signals, most commonly in the form of action potentials. Though there is a rich body of theoretical work proposing various forms of single neuron computations, experimental data to test these models by measuring input and output during

behavior are lacking. This is in part because inputs are distributed over the large volume spanned by a neuron's dendrites, making optical recording of excitatory synaptic activity, for example using glutamate imaging, challenging. We developed a new high-speed two-photon microscope, SLAP2, that is able to record dendritic arbors with high spatial resolutions at over 100 Hz. SLAP2 combines a line scanner, two digital micromirror devices (DMDs), and remote focusing to allow fast and flexible random-access scanning simultaneously over two 3D volumes of approximately 200x300x500 μm each. SLAP2 enables a new fast mode of imaging ("integration mode") where fluorescence along the scanned line is summed. We have created an analysis pipeline that identifies fluorescent indicator activity in integration mode data. Motion correction, based on robust measures of comparison to a z-stack, can be run online or offline. Source detection is based on projecting the data into a pixel space and performing matrix factorization. We validated our pipeline in simulations and with *in vivo* recordings of dendrites expressing the genetically-encoded fluorescent glutamate indicator iGluSnFR3. We used this system to simultaneously measure glutamatergic inputs to a neuron using glutamate indicators and firing output from a neuron using calcium indicators (e.g. jRGECO1a). We expect to measure signals from up to 1000 synapses at 100 Hz, representing ~15% of a L2/3 cortical neuron's synapses. We will present input-output measurements of a single cortical neuron in behaving mice and detail our hardware and software. Our technology enables comprehensive study and characterization of single-neuron computations *in vivo*.

Disclosures: M.E. Xie: None. **A. Negrean:** None. **L. Kinsey:** None. **G. Jaindl:** A. Employment/Salary (full or part-time):; MBF Bioscience. **A. Charles:** None. **K. Podgorski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent inventor, Scanned Line Projection Microscopy. **K. Svoboda:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.11/A75

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: R21

Title: Single-cell multi-omics and synaptic imaging of the post-mortem cerebellum to assess dysregulation of neural-glial interactions in schizophrenia and bipolar disorder.

Authors: *M. E. CORTES-GUTIERREZ[1], A. BISWAS[4], R. O'HARA-PAYNE[5], J. MAUBAN[2,3], R. SCHWARCZ[8], R. JOHNSON[9], J. SIVINSKI[2], T. A. BLANPIED[6], S. A. AMENT[7];
[1]Inst. for Genomes Sci., [3]Physiol., [2]Univ. of Maryland, Baltimore, MD; [4]Univ. of Maryland, Baltimore, Baltimore, MD; [5]Program in Epidemiology and Human Genet., [6]Dept. of Physiol.,

[7]Dept. of Psychiatry and Inst. for Genome Sci., Univ. of Maryland Sch. of Med., Baltimore, MD; [8]Psychiatry, [9]Maryland Psychiatric Res. Ctr., Baltimore, MD

Abstract: It has long been postulated that changes in synaptic structure and function contribute to the etiology of psychiatric disorders, but a detailed understanding has been delayed by the technical challenges in profiling human brain tissue. Here, we applied single-nuclei multi-omic, spatial transcriptomic, and high-resolution imaging techniques to characterize cell type-specific gene networks in the post-mortem brains of donors with schizophrenia and bipolar disorder and the relationships of these gene networks with quantified synaptic features. We focused on the cerebellar vermis, owing to its well-characterized and relatively uniform synaptic organization, as well as longstanding evidence for its neuroanatomical differences in individuals with psychiatric disorders. We studied the transcriptomes and accessible chromatin states in 296,399 cells from the post-mortem cerebellar vermis of 16 donors who died with schizophrenia, 16 with bipolar disorder, and 20 controls with no mental illness. Many of the most strongly differentially expressed genes (False Discovery Rate < 0.05) comprised synapse-associated gene networks expressed in Purkinje cells, granule cells, and Bergmann glia. Together, these three cell types comprise the tripartite synapses of parallel fibers onto Purkinje cells, the most abundant synapses in the molecular layer of the cerebellum. We correlated these transcriptomic features with molecular phenotypes quantified in the peri-synaptic area. We found that cell adhesion molecules and their receptors, such as ROBO2 and SLIT2, were coordinately dysregulated across neural and glial synaptic components. These cell adhesion molecules mediate dynamics of dendritic branching and synaptic organization, contributing to the formation, pruning, and stabilization of synaptic contacts during development, to, as well as the maintenance of these contacts during adult life. Abnormal configurations of these neural-glial contacts at parallel fiber—Purkinje cell synapses may contribute to altered cerebellar functions in psychiatric disorders.

Disclosures: M.E. Cortes-Gutierrez: None. **A. Biswas:** None. **R. O'Hara-Payne:** None. **J. Mauban:** None. **R. Schwarcz:** None. **R. Johnson:** None. **J. Sivinski:** None. **T.A. Blanpied:** None. **S.A. Ament:** None.

Poster

PSTR103: Somatic and Dendritic Integration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.12/A76

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH grant R01EY035268

Title: Metabotropic glutamate receptor 2 (mGluR2) mediates activity-dependent modulation of dendritic excitability in starburst amacrine cells

Authors: *S. OOSTERBOER[1], J. TIJERINA[1], Z. DENG[1], S. WANG[2], W. WEI[3];
[1]The Univ. of Chicago, Committee on Neurobio., Chicago, IL; [2]Stanford Univ. Sch. of Med., Palo Alto, CA; [3]Dept. of Neurobio., The Univ. of Chicago, Chicago, IL

Abstract: Dendrites shape the input-output relationship of a neuron. The starburst amacrine cell (SAC) in the mouse retina serves as an excellent model to study dendritic computation. The radially and symmetrically oriented dendrites of SACs are tuned to an outward motion within each dendritic branch. The direction selectivity of SAC dendrites is crucial for the direction selectivity of their postsynaptic partners, the direction selective ganglion cells, which transmit motion signals from the retina to the brain.
SACs express metabotropic glutamate receptor type 2 (mGluR2), and mGluR2 signaling plays an important role in maintaining SAC direction selectivity. The goal of this study is to determine the role of activity-dependent mGluR2 signaling in SAC dendritic computation. Since glutamate release from bipolar cells onto SACs is visual activity-dependent, we hypothesized that mGluR2 signaling in the SAC is modulated by visually evoked glutamate release, which in turn leads to modulation of dendritic calcium channel activity. To test this hypothesis, we use whole-cell voltage recording to study voltage-gated calcium current threshold in SACs under different visual stimulus conditions. We found that visual stimulation with a flickering checkerboard causes a significant shift in voltage-gated calcium channel threshold in SACs. This activity-dependent shift of threshold is blocked by mGluR2 antagonist. These results show that visual evoked glutamate released from bipolar cells can modulate the calcium channel threshold in SACs through mGluR2 signaling, indicating that mGluR2 mediates homeostatic regulation of dendritic excitability according to synaptic activity.

Disclosures: S. Oosterboer: None. **J. Tijerina:** None. **Z. Deng:** None. **S. Wang:** None. **W. Wei:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH grants 1R01NS133755
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Chan Zuckerberg Initiative grant 2023-321177
Harvard-MIT Joint Research Grant in Basic Neuroscience
Brain Research Foundation
National Research Foundation of Korea

Title: Mapping voltage dynamics of dendritic arbor in live behaving mice

Authors: *B. LEE[1], P. PARK[2], X. WU[2], D. WONG-CAMPOS[2], A. E. COHEN[2];
[2]Dept. of Chem. and Chem. Biol., [1]Harvard Univ., Cambridge, MA

Abstract: Dendrites receive widely distributed synaptic input and convert to action potential output within a complex, non-linear framework. Despite dendrites thought to serve as critical processing units, the in vivo mechanism of dendritic information processing and plasticity remain elusive. In this study, using high-speed voltage imaging through a chronically implanted microprism, we visualized membrane potential dynamics from basal to apical distal dendrite of CA1 neuron in mice navigating the virtual reality. We found highly correlated activity between basal dendrites, but apical and basal dendrites showed distinct activities. We examined the dendritic subthreshold dynamics and their role in eliciting distinct spike phenotypes: complex spikes, simple spikes, and dendritic spikes (dSpike). These results widen the understanding how CA1 pyramidal neuron computes external sensory input and internal spatial information and underlying learning and memory process.

Disclosures: B. Lee: None. **P. Park:** None. **X. Wu:** None. **D. Wong-Campos:** None. **A.E. Cohen:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Program #/Poster #: PSTR103.14/A78

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant R01-NS126043
NIH Grant R01-MH117042
Harvard Brain Science Initiative
Chan Zuckerberg Initiative

Title: Dendritic integration and plasticity rules revealed by simultaneous voltage and Ca^{2+} imaging in vivo

Authors: *X. WU, B. LEE, D. WONG-CAMPOS, P. PARK, A. E. COHEN;
Chem. and Chem. Biol., Harvard Univ., Cambridge, MA

Abstract: As the conduits of information between synapses and soma, neuronal dendrites play important roles in determining neuronal integration and synaptic plasticity. Theoretical and *in vitro* studies showed that dendrites support regenerative events such as dendritic spikes and plateau potentials, but the computational significance of these events *in vivo* is not known. Direct measurements of dendritic excitations have been difficult to obtain *in vivo*, mainly due to the lack of techniques to simultaneously map the dendritic voltage and Ca^{2+} dynamics in live animals. As a result, it remains unclear when and where these dendritic events happen *in vivo*, how they are related to animal behavior, and why they occur. To decipher the roles of active dendrites *in vivo*, we performed simultaneous imaging of voltage and Ca^{2+} dynamics in neuronal

dendrites and somas of hippocampal place cells in navigating mice. We developed a high-speed dual-channel spinning disk confocal microscopy system with patterned illumination, which provided superior imaging quality and signal-to-noise ratio compared to wide-field microscopy commonly used for voltage imaging. To provide optical access to the entire dendritic tree of CA1 pyramidal neurons, we implanted an elongated microprism into the mouse hippocampus. We mapped the subthreshold and suprathreshold dendritic voltage and Ca^{2+} dynamics as a mouse navigated in a virtual reality environment. This works provides new insights into the role of active dendrites in neuronal integration and synaptic plasticity.

Disclosures: X. Wu: None. **B. Lee:** None. **D. Wong-Campos:** None. **P. Park:** None. **A.E. Cohen:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.15/A79

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Title: Nmda receptors control pathway-specific visual information in l2/3 pyramidal cells

Authors: *V. J. OLAH[1], M. J. ROWAN[2];
[1]Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA; [2]Dept. of Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Understanding sensory information processing has been one of the central aims of neuroscience. However, the extent to which subcellular information processing shapes single-neuron contributions to sensory information processing still needs to be fully resolved. This is particularly true for one of the most numerous cell populations of the central nervous system, the layer 2/3 pyramidal cells (L2/3 PCs). We have previously shown that L2/3 PCs express functionally relevant hyperpolarization-activated nonselective cation (HCN) channels, which constrain neuronal excitability by altering resting membrane potential and input resistance. Our results show that contrary to L5 PC, HCN channels are located in proximal somatodendritic surfaces. Therefore, their function cannot be consistent with distance-dependent normalization. Instead, this unique HCN distribution yields a regulatory effect biased towards information from bottom-up synaptic pathways instead of top-down information. Interestingly, simulation experiments suggest that our experimental findings can only be recapitulated if NMDA receptors have a similar, proximal localization whereby HCN channels provide a shunting effect over NMDA receptors in baseline conditions. Using NMDA pharmacology combined with stimulating axon fibers in either Layer 1 or 4, we have now confirmed these simulation results. Like other cortical areas, in the visual cortex, top-down and bottom-up information mainly terminates in well-separated cortical layers (layer 1 and layer 4, respectively), which suggests that feed-forward and feed-back visual pathways can differently recruit NMDA receptors. We investigated this possibility using optogenetics, by injecting the red-shifted opsin C1V1 into

either visual primary thalamus (lateral geniculate nucleus; LGN) or a higher-order cortical area (lateromedial cortex; LM). We found that activation of the L1 terminating 'top-down' LM fibers did not recruit a substantial amount of NMDA receptors, while proximal terminating 'bottom-up' LGN fibers elicited a synaptic response that was sensitive to NMDA blockers. Next, we employed a novel CRISPR-based anatomical method (TKIT) to confirm our findings anatomically. This approach labels native GluN1 or GluN2A NMDA receptor subunits. Examining the occurrence of fluorescently labeled (i.e., NMDA+) spines in identified L2/3 PCs, we found that NMDA receptors are indeed more abundantly expressed in proximal dendritic locations. Our results demonstrate that layer 2/3 pyramidal cells utilize HCN channels and NMDA receptors conjointly to modulate pathway-specific visual information in a previously unobserved manner.

Disclosures: V.J. Olah: None. **M.J. Rowan:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH DP2MH136494
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AFOSR FA9550-23-1-0701
NSF #2120200 EMBRIO Institute

Title: Distinct somato-dendritic coupling dynamics in anatomically defined L5B pyramidal neuron subtypes

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[1]Purdue Univ., West Lafayette, IN; [2]Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN; [3]Purdue institute for integrative neuroscience, Purdue University, West Lafayette, IN

Abstract: Integrating bottom-up and top-down inputs in the sensorimotor cortices is crucial for accurate sensory perception. The layer 5 pyramidal neurons (L5PNs) play a central role in this framework, with their elaborate dendritic trees integrating long-range feedback in superficial tuft dendrites and feedforward inputs across the basal regions. It is important to note that L5PNs are divided into two subpopulations - L5A and L5B - based on morphology, anatomy, and genetics. Recent evidence suggests that L5B PNs can be further divided into non-overlapping subgroups, and yet little is known about the integration properties across these subtypes. We performed two-photon visually guided dual somato-dendritic patch-clamp recordings and two-photon calcium imaging in L5BPNs from the mouse barrel cortex in acute brain slices to investigate this. Through retrograde labeling, we identified L5BPNs with different downstream projections and

revealed unique morphology and physiology. Specifically, pons-projecting L5BPNs were demarcated by early apical dendritic bifurcation and intrinsically bursting (IB) patterns. In contrast, posteromedial thalamic nucleus (POm) and superior colliculus (SC)-projecting L5BPNs revealed bifurcations in superficial layers, burst rarely and exhibited regular spiking (RS) characteristics. Our findings indicate less apical dendritic compartmentalization in pons-projecting L5BPNs compared to Pom and SC-projecting L5BPNs, including larger back-propagating action potentials (bAPs) and a lower threshold of bAP-activated calcium bursts, which are hallmarks of translaminar integration and accurate sensory perception. Under *in-vivo*-like conditions, enabled via a dynamic clamp, global bursts in IB L5BPNs appeared to perform a "resonator" like function aided by the noisy background. In contrast, RS L5BPNs performed reliable coincidence detection only upon strong and synchronous apical inputs. Using multicompartment biophysical simulations, we found that along with the unique bifurcation of the main apical dendrite, the distribution of Na^+ channels and their rate of recovery from inactivation across the soma-apical axis is a key factor in regulating the compartmentalized characteristics and burstiness in these projection sub-types. Finally, early-stage results via two-photon calcium imaging *in vivo* highlight distinct top-down dendritic integration dynamics across these projection classes. Our findings suggest a critical role for somato-dendritic coupling in coordinating and broadcasting different top-down sensorimotor integration strategies across subcortical networks.

Disclosures: S. Xiao: None. **J. Morris:** None. **K. Jayant:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH 1RM1NS132981-01

Title: Unveiling the biophysical and morphological properties of dendritic spines from high-resolution whole-cell dense reconstruction of cortical pyramidal neurons

Authors: *N. OFER[1], S. SHAPIRA[2], M. ABDELLAH[3], I. SEGEV[4];
[1]Brain Sci. - ELSC, [2]The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]Blue Brain Project, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; [4]Inst. of Life Sciences, Hebrew Univ., Jerusalem, Israel

Abstract: The dendritic tree of cortical pyramidal neurons is densely decorated with thousands of dendritic spines. These small protrusions, composed of thin necks and bulbous heads of widely varying sizes, are the targets for excitatory synapses where key nonlinear and plasticity processes occur. However, the integration of excitatory synaptic inputs across these dendritic spines, and especially, how distal excitatory synapses affect the neuron’s output, remains a

pivotal unanswered question in neuroscience. In this study, we utilized, for the first time, a dense nano-scale reconstruction from serial section electron microscopy (EM) of entire pyramidal neurons. Our database includes hundreds of neurons from both mice and humans, each equipped with thousands of spines, allowing us to systematically investigate the morphological properties of dendritic spines across the entire dendritic surface of cortical pyramidal neurons. Utilizing high-resolution 3D reconstruction, we accurately measured the morphological parameters of the dendritic spines, including neck length, average neck diameter, and head volume for each spine (Ofer et al., 2021). We developed a new method to estimate the electrical resistance (R_{neck}) of the spine neck, whose diameter undergoes repeated changes, based on a series summation of nanoscale segments orthogonal to the spine neck. We discovered that (i) R_{neck} estimated using the conventional method that considers the average neck diameter may significantly underestimate the actual Rneck value; (ii) the ratio between spine neck resistance and the input resistance at the spine base (R_{base}) is not random. Furthermore, we found that, on average, spine-neck resistances increase with distance from the soma. Our results lend support to the theoretical study by W. Rall (1974), proposing a novel design principle for optimal gain control over the impact of spinous excitatory synapses by matching the ratio R_{neck}/R_{base} per spine. This EM-based computational study casts new light on the structure-to-function implications of dendritic integration in cortical pyramidal cells. Ofer N, Berger DR, Kasthuri N, Lichtman JW, Yuste R (2021) Ultrastructural analysis of dendritic spine necks reveals a continuum of spine morphologies. Dev Neurobiol 81:746-757. Rall W (1974) Dendritic spines synaptic potency and neuronal plasticity. In: Cellular mechanisms subserving changes in neuronal activity (Woody CD, Brown A, Crow TJ, Knispel JD, eds), pp 13-21. Los Angeles (Brain information research report): University of California.

Disclosures: N. Ofer: None. **S. Shapira:** None. **M. Abdellah:** None. **I. Segev:** None.

Poster

PSTR103: Somatic and Dendritic Integration

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Program #/Poster #: PSTR103.18/B3

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH 1RM1NS132981-01

Title: Impact of dendritic spines on temporal information processing: insights from electron microscopy-based computational study.

Authors: *S. SHAPIRA[1], N. OFER[2], M. ABDELLAH[3], I. SEGEV[4];
[1]The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]ELSC, The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]Blue Brain Project, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; [4]Inst. of Life Sci., Hebrew Univ., Jerusalem, Israel

Abstract: Dendritic spines, minuscule dendritic branches with thin (~100 nm) necks and bulbous heads, serve as the primary sites of excitatory synaptic inputs in cortical pyramidal neurons. These structures are hypothesized to play crucial computational roles by electrically and chemically isolating synaptic inputs from one another, fostering unique microenvironments that enhance synaptic plasticity. Dendritic spines also facilitate synaptic connections among neurons and unify the properties of local excitatory postsynaptic potentials (EPSPs) at the spine head membrane, where synaptic input is received. This study utilizes nanometer-scale electron microscopy (EM) reconstructions of approximately 9,000 dendritic spines from both human and mouse L2/3 pyramidal neurons to explore their roles in temporal information processing. Employing simulations that incorporate detailed EM reconstructions of whole pyramidal neurons, each with several thousand spines, alongside abstract neuronal models, we demonstrate the crucial role of spine neck morphology in facilitating ultrafast conversion (within the sub-millisecond range) of synaptic currents into local voltage signals (EPSPs) at the spine head membrane. This rapid signaling capability allows dendritic spines to accurately respond to modulated synaptic inputs at kHz frequencies. This responsiveness is highly sensitive to slight variations in spine neck diameter within biologically ranges, as found by our EM data. Moreover, the high density of dendritic spines along the dendritic arbor (ranging from 0.5 to 4 spines per 1 µm dendritic length) affects signal propagation along the dendrites. Near the spine receiving the excitatory synaptic input, signal propagation is particularly fast, favoring synchronous inputs adjacent to the input spine for enhancing signal amplification through local nonlinear voltage interactions (e.g., via NMDA receptor). Conversely, at a more global level, increased spine density decelerates the propagation of synaptic potentials from the input synapse to the soma, illustrating a complex interplay between local enhancement of spine-to-spine interactions and global reduction in signal propagation speed with increased spine density. This EM-based computational study reveals new insights into the local (branch-specific) and global (whole-tree) impacts of dendritic spines and their precise morphology on signal processing in cortical pyramidal cells.

Disclosures: S. Shapira: None. **N. Ofer:** None. **M. Abdellah:** None. **I. Segev:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.01/B4

Topic: B.09. Glial Mechanisms

Support: HMN Grant 28293
FFU Grant 34226

Title: Transcriptome profiling of cortical astrocytes and neurons upon sustained local noradrenergic neuromodulation

Authors: *M. DAHLE, S. FJELDSTAD, N. LIABAKK, E. JOHANNESSEN STARHEIM, W. TANG;
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Abstract: The noradrenergic neuromodulatory system is essential for regulating important brain functions, such as arousal, attention, and learning. Yet, how noradrenalin (NA) influences different cell types at the level of the transcriptome is still inadequately elucidated. The main noradrenergic output originates from Locus Coeruleus (LC) in the pons of the brainstem, projecting widely within the brain. During prolonged periods of stress, the activity of LC neurons, as well as their release of NA, increases. This will in turn affect their downstream targeted neurons and astrocytes. In this study, we aim to determine changes in gene expression profiles in mouse somatosensory cortical astrocytes and neurons, during long-term enhanced NA modulation. To achieve this, we have combined the use of rAAV-mediated gene delivery, chemogenetics, and RNA sequencing (RNA-seq). We have developed a novel method for activating distinct LC neurons projecting to somatosensory cortex, using a combination of split-Cre complementation and DREADDs via rAAV gene delivery. In addition, experimental procedures for preparing both nuclear and whole-cell RNA from NA-modulated somatosensory cortical tissues for RNA-seq have been established. These methods are powerful to investigate the impact of the noradrenergic neuromodulatory system, and to obtain transcriptomic data from their downstream targets, both neurons and astrocytes. Moreover, results from bulk RNA-seq of astrocytes and neurons will provide further insight into the sustained NA modulatory effect, revealing changes in gene expression occurring within the distinct cell populations.

Disclosures: M. Dahle: None. **S. Fjeldstad:** None. **N. Liabakk:** None. **E. Johannessen Starheim:** None. **W. Tang:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

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Program #/Poster #: PSTR104.02/B5

Topic: B.09. Glial Mechanisms

Support: HMN Grant 28293
FFU Grant 34226

Title: Transcriptome profiling of cortical astrocytes and neurons upon silencing of local noradrenergic neuromodulation

Authors: *S. FJELDSTAD, M. DAHLE, N.-B. LIABAKK, E. JOHANNESSEN STARHEIM, W. TANG;
Dept. of Clin. and Mol. Med., Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: Brain noradrenergic neuromodulation is crucial in healthy brain function. The release of noradrenaline governs a wide range of global brain state changes. The main source of

noradrenaline in the brain is the Locus Coeruleus (LC). LC neurons release noradrenaline through both synaptic transmission and global volume transmission. In addition to neurons, brain astrocytes also express various noradrenergic receptors. Astrocytes cover large volumes across the extrasynaptic space in the brain, and have hence been proposed as an important additional target of noradrenaline. The effect of noradrenaline on neural circuits and animal behavior have been extensively studied, however, the detailed molecular changes at the transcriptomic level of targeted astrocytes and neurons remain poorly understood. In order to study the impact of noradrenergic neuromodulation on somatosensory cortical astrocytes and neurons, we utilized a rAAV delivered Split-Cre complementation system in combination with rAAV-retro serotype, to specifically target LC neurons projecting to the somatosensory cortex (SC) in mice. To deactivate LC neurons, a chemogenetic silencing tool was introduced to suppress LC neuronal activity and their noradrenaline release. The receptor introduced is a chlorine ion channel that is gated by the common anthelminthic drug Ivermectin (IVM). After IVM treatment, nuclei from astrocytes and neurons in SC were isolated and sorted via FACs. Both astrocytic and neuronal nuclei RNA was extracted for bulk RNA-seq. Our study further explores the transcriptomic profiles of SC astrocytes and neurons before and after LC neuronal silencing. In addition, our study has established a novel method to target and manipulate LC neurons projecting to defined brain regions.

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Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

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Program #/Poster #: PSTR104.03/B6

Topic: B.09. Glial Mechanisms

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Title: Astrocytes mediate the effect of norepinephrine at excitatory synapses

Authors: *K. LEFTON[1], Y. WU[2], A. YEN[3], Y. ZHANG[4], S. WALSH[5], Y. DAI[2], J. D. DOUGHERTY[6], V. K. SAMINENI[7], T. PAPOUIN[8];
[1]Neurosci., Washington Univ. in St. Louis Neurosci. PhD Program, St. Louis, MO; [2]Neurosci., Washington Univ. in St. Louis, St. Louis, MO; [3]Genet., Washington Univ. Sch. of Med., Saint Louis, MO; [4]Washington Univ. in St. Louis, St Louis, MO; [5]Neurosci., Washington Univ. Sch. of Med., Maryland Heights, MO; [6]Washington Univ. Sch. of Med., St. Louis, MO; [7]Washington

Univ., St Louis, MO; [8]Neursocience, Washington Univ. in St Louis, Dept. of Neurosci., St. Louis, MO

Abstract: Astrocytes are known to respond to norepinephrine (NE) neuromodulation with a robust calcium response, driving intense speculation to the circuit and behavioral relevance of astrocytes in NE-dependent processes. Surprisingly, the significance of this responsiveness to the circuit effects of NE neuromodulation, however, has remained unaddressed. In the cortex and hippocampus, NE induces a profound change in circuit connectivity, in part via its well-documented dampening of synaptic efficacy. Here we report that NE modulates synaptic networks by signaling entirely through astrocytes. Indeed, we find that scavenging endogenous adenosine or blocking adenosine A1 receptors (A1R) abolishes the effect of NE on excitatory synapses in adult (P100) mouse hippocampal slices. In the hippocampus, A1Rs are predominantly expressed pre-synaptically and are negatively coupled to release probability. Consistently, we find that the effect of NE on synaptic transmission is mediated by a decrease in pre-synaptic release probability. Furthermore, we find that NE applications are without effect on synaptic strength in slices obtained from mice lacking the ATP-adenosine converting enzyme, CD73. Together, this indicates that, rather than a direct effect, NE modulation of synaptic efficacy leverages ATP-adenosine signaling. Astrocytes are a major source of extracellular ATP, and astrocyte-derived ATP release is Ca^{2+}-dependent. Therefore, we sought out to test directly the role played by astrocytes in the effect of NE on synaptic function. We find that interfering with astrocytic Ca^{2+} activity using IBARK, CalEx, or pharmacological approaches entirely abolishes the effect of NE on synapses. We further show that knocking out alpha1a noradrenergic receptors from astrocytes, but not neurons, entirely blocks the inhibitory effect of NE on synapses. Combined, our findings fuel the notion that NE neuromodulation remodels synaptic networks via an entirely indirect, astrocyte-dependent mechanism rather than by acting directly through neuronal noradrenergic receptors.

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Poster

PSTR104: Astrocyte Cell Biology

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Topic: B.09. Glial Mechanisms

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Presupuesto interno de la Facultad de Medicina UNAM

Title: The $GABA_A$receptors modulate VEGF release and synthesis in Müller glial cells

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Abstract: $GABA_A$ receptor activation in glial cells has been described as an effector of cellular depolarization capable of inducing growth factor secretion. Müller glial cells, the main glial cells in the retina, support homeostasis in this tissue; however, the functions of GABA receptors in Müller glial cells, beyond the gliotransmission, are not fully understood. Moreover, Müller glial cells are the main source of VEGF in the neuro-retina. Few studies indicate a possible relationship between the GABAergic system and VEGF, without being conclusive. For this reason, the goal of this study was to explore the effect of GABA on VEGF synthesis and release from Müller glia cells, and the possible cellular mechanism involved. Primary cultures of Müller cells from CD1 mice were exposed to GABA (1-200 µM) or $GABA_A$ receptor agonists (muscimol) for 48 hours, in the presence or absence of gabazine, a $GABA_A$ antagonist. We also explored a signaling pathway involving extracellular calcium entry via L-type Calcium Channels (LTCC) and the subsequent ERK1/2 phosphorylation and HIF-1α nuclear translocation. VEGF synthesis and release were quantified by immunofluorescence and ELISA. Our results show that GABA induces a significant decrease in VEGF release but promotes an increase in VEGF synthesis. These opposing effects are dependent on GABA concentrations and were significant at 100 µM. Interestingly, activation of the $GABA_A$ receptor through muscimol has a similar effect to GABA, and gabazine inhibits these responses. Moreover, extracellular calcium depletion by Ringer-Krebs medium Ca^{2+}-free, BAPTA-AM, and the LTCC blocker nimodipine inhibits VEGF responses to GABA. Similar results were shown for ERK phosphorylation inhibition by FR180204. Finally, immunofluorescence assays showed that HIF-1α accumulates in Müller glial cell nuclei treated with GABA and muscimol. Taken together, these data suggest that $GABA_A$ receptors have a role in the regulation of VEGF release and synthesis mechanism in mouse retinal Müller glial cells involving the extracellular Ca^{2+}/LTCC/ERK1/2/HIF1α/VEGF signaling pathway. This interaction would contribute to a better understanding of retinal vasoproliferative diseases, where it appears that the $GABA_A$ receptors may play a role in the vasoproliferative context.

Disclosures: A. Medina Arellano: None. **L.D. Ochoa-De La Paz:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.05/B8

Topic: B.09. Glial Mechanisms

Title: The role of mulberry leaf extracts and quercetin for glycogen accumulation in astrocytes

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Abstract: The astrocyte-neuron lactate shuttle (ANLS) is said to play an important role in the regulation of energy metabolism in the brain. ANLS is a mechanism by which glucose in the blood is taken up by astrocytes, converted to lactic acid, and supplied to neurons to maintain brain function. At steady state, astrocytes convert a portion of glucose into glycogen. It is believed that when neurons activate, glycogen is converted to lactate, which is then supplied to neurons as an energy source. Mulberry leaf extracts are known to increase glycogen levels in the muscle, and mulberry leaf extracts may also effects glycogen accumulation in astrocytes. In this study, we evaluated whether mulberry leaf extracts promote an increase in glycogen in human-induced pluripotent stem cell (hiPSC) derived astrocytes and explored the functional substances. The results showed that mulberry leaf extracts promoted glycogen accumulation. Moreover, several quercetin glycosides in mulberry leaf extracts exerted some of the activity of the extracts. Quercetin aglycones, the basic compound structural backbone without glycosides, also increased glycogen. To confirm that this glycogen store can be converted to lactate, hiPSC-derived astrocytes were incubated under glucose-free medium one day after treatment with quercetin aglycones. As a result, glycogen was degraded and lactate production increased with quercetin aglycones compared to without them. In conclusion, we found that quercetin aglycones may activate ANLS.

Disclosures: H. Arie: None. **K. Nishioka:** None. **T. Suzuki:** None. **Y. Nakamura:** None. **T. Azuma:** None. **T. Yamagaki:** None. **N. Murayama:** None.

Poster

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Program #/Poster #: PSTR104.06/B9

Topic: B.09. Glial Mechanisms

Support: FAPESP Grant 2021/12832-7
FAPESP Grant 2013/07699-0
CNPq Grant 303235/2018-7

Title: Dopamine facilitates glutamatergic input response in astrocyte cell computational models

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Abstract: Astrocytes are active cells that respond to neurotransmitters with intracellular calcium signals. In a tripartite synapse, glutamate release by the presynaptic neuron can induce astrocytic

calcium signals, triggering gliotransmitter release that modulates synaptic transmission. Additionally, dopamine released by distant sites also can evoke astrocytic calcium signals, but little is known about dopamine's modulatory effects on glutamatergic-evoked astrocyte activity. To address this question from a computational neuroscience point of view, we constructed compartmental models of astrocytes with different morphologies to study how local glutamatergic and global dopaminergic inputs interact and influence the intracellular calcium concentration. Compartments were modeled by conductance-based equations for membrane voltage and transport of ions, glutamate and dopamine between extra- and intracellular spaces, interconnected by diffusion. Both glutamate and dopamine activate metabotropic receptors on the astrocyte membrane, promoting calcium release from endoplasmic reticulum by an IP3-dependent mechanism. In addition, glutamate also promotes calcium influx by a glutamate transporter-dependent mechanism. Additionally, we developed a simplified two-variable version of the astrocyte compartment model to study the interplay between compartment radius and glutamate and dopamine stimulation rates. Our simulation results show that dopamine facilitates glutamatergic-evoked calcium signals in all astrocytic morphologies studied. Furthermore, calcium and IP3 dynamics are distinct for compartments with different radii. Calcium signals proximal to the soma have spike-like shapes, whereas at distal compartments they are less pronounced, with IP3 accumulating predominantly in distal compartments and diffusing to nearby ones. A phase-plane analysis of the simplified model revealed that compartment radius serves as a threshold parameter for the generation of calcium signals. Moreover, for thicker compartments two different behaviors were observed depending on the stimulating neurotransmitter. While a threshold glutamatergic input rate was identified for the generation of calcium signals, dopaminergic stimulation was less effective than glutamatergic stimulation in isolation. However, concurrent application of both glutamate and dopamine stimulation enhanced the effect of glutamatergic input. Our findings indicate a dopamine role in facilitating glutamatergic-evoked calcium signals and suggest a potential mechanism for regulating the distribution of calcium signals within astrocytic processes.

Disclosures: T. Ohno Bezerra: None. **A.C. Roque:** None.

Poster

PSTR104: Astrocyte Cell Biology

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Program #/Poster #: PSTR104.07/B10

Topic: B.09. Glial Mechanisms

Support: KAKENHI Grant 24KJ2184

Title: Elucidating mechanisms of astrocytic depolarization

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Abstract: The electrophysiological properties of brain cells are the foundation of learning and plasticity. For the past century, neurons have been thought to be the only cell type with these dynamic electrical properties. As dynamic changes in membrane potentials are how neurons propagate information, other non-neuronal cells, otherwise known as glia, were considered irrelevant. Astrocytes, which account for more than half of glial cells in the human brain, have similarly shown passive responses to classical electrophysiological techniques. Recent reports utilizing fluorescent voltage indicators show dynamic changes in astrocytic membrane potentials occurring only at peripherals contacting synapses[1]. The astrocytic depolarization occurs as a response to potassium elevation induced by neuronal activity. Depolarization can affect astrocyte functionality and synaptic plasticity by altering how neurotransmitters diffuse through the synaptic cleft[1,2]. As astrocytes contact thousands of synapses, this suggests astrocytes affect information processing within large populations of neurons, with unknown implications. Unfortunately, the sites where neurons and peri-synaptic astrocytic processes (PAPs) interact are below the light diffraction limit, hindering observation and research. Therefore, it is unknown how depolarization of PAPs is induced/maintained and how these mechanisms affect the brain's information processing. Utilizing mechanistic models, we theoretically explored how the relationship between extracellular potassium and astrocytic channels, such as Kir 4.1 and NMDA receptors, can induce PAP depolarization. Our simulations reveal how these two channels cooperate to produce focal depolarizations that are not possible independently. These simulations also revealed how an imbalance between channels leads to abnormalities in astrocytes. As our model suggests that PAP depolarization is responsive to physiological neuronal activity, we next examined the implications of PAP depolarization on short-term synaptic plasticity. Preliminary results show that PAP depolarization can indeed alter neurotransmitter dynamics within the synaptic cleft.
1. Armbruster M. et al. (2022) Neuronal activity drives pathway-specific depolarization of peripheral astrocyte processes, *Nat. Neurosci*.
2. O'Kane. et al. et al. (1999) Na+-dependent Glutamate Transporters (EAAT1, EAAT2, and EAAT3) of the Blood-Brain Barrier, *Cell Biol. Met.*

Disclosures: R.J. Nakatani: None. **E. De Schutter:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

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Topic: B.09. Glial Mechanisms

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CIHR PJT-159779
ExCELLS 23-S2
NIPS 22-161, 23-155, 24-127

Title: Astrocytic processes wrap orexin and non-orexin neurons in the lateral hypothalamus: Ultrastructural analysis and implications for the tripartite synapse

Authors: *K. SEMBA[1], J. BURNS[1], C. BRIGGS[1], T. GOLOVIN[2], S. HATADA[3], S. DEURVEILHER[1], C. SOZUER[1], Y. KUBOTA[3,4,5];
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Abstract: Astrocytes play important roles in various brain functions including synaptic plasticity. For sleep regulation, we previously reported astrocyte-mediated, sleep history-dependent synaptic plasticity in wake-promoting orexin (hypocretin) neurons in the rat lateral hypothalamus (LH; Briggs et al., 2018, J Neurosci) and identified structural remodeling of perisynaptic astrocytic processes as one mechanism underlying this plasticity, by using correlative light-electron microscopy (EM) and serial EM reconstruction (Semba et al., 2023, SfN). During the course of the latter study, we observed that much of the surface of the somata and proximal dendrites of orexin neurons is covered by astrocytic processes which are often as thin as ~100 nm. The continuity of astrocytic coverage is interrupted where synapses are made by axon terminals; at these synaptic sites, astrocytic processes step away from the orexin neuron and often surround the presynaptic terminal, while typically participating in tripartite synapses. Similar astrocytic coverage of the soma is observed in non-orexin LH neurons intermixed with orexin neurons. Preliminary quantitative analyses of serial EM sections indicate that the astrocytic coverage of the surface of orexin neurons (soma and proximal dendrites) ranges from 67-74% (n=4), while it is 49-77% (n=3) after 6 h of sleep deprivation (SD). The astrocytic coverage of non-orexin neurons is similar to that with orexin neurons, ranging from 52-77% (n=4) at rest, and 73-83% (n=3) after SD. Finally, preliminary inspections of serial EM sections indicate that single thin astrocytic processes typically approach multiple synapses to the same orexin neuron, as well as those to non-orexin somata and dendrites and, occasionally, a blood vessel. These observations indicate that orexin and some non-orexin LH neurons are extensively covered with astrocytic processes and sheets often only 100 nm in thickness. This astrocytic covering is disrupted where axon terminals approach and make synaptic contacts with neurons. The unusually extensive astrocytic coverage of LH neurons raises questions about its functions as well as its possible roles in the formation and regulation of tripartite synapses.

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Poster

PSTR104: Astrocyte Cell Biology

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Program #/Poster #: PSTR104.09/B12

Topic: B.09. Glial Mechanisms

Support: NSERC Discovery Grant
FRQS postdoctoral fellowship

Title: Subtypes of astrocytes regulate specific hippocampal inhibitory synapses

Authors: *D. CLARKE[1], A. BOSSON[2], E. HONORÉ[3], E. AVIGNONE[4], J.-C. LACAILLE[1], R. ROBITAILLE[1];
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Abstract: Astrocyte functional heterogeneity within a given neuronal circuit remains largely undetermined, particularly their role at tripartite synapses. Here, we examine multiple functional characteristics of astrocytes distinguished by their specific spatial relation to inhibitory synapses made on distinct hippocampal CA1 pyramidal cell domains: astrocytes covering the peri-somatic area in *stratum pyramidale* (SP) receiving input from Parvalbumin interneurons, or the apical dendritic area in *stratum radiatum* (SR) innervated by inhibitory inputs from Somatostatin interneurons. Whole-cell dye-filling and confocal imaging showed a typical bushy organization of SR astrocyte processes while those of SP astrocytes were more polarized, indicating astrocyte morphological heterogeneity. In addition, SR astrocytes formed a larger syncytium and displayed lower input resistance relative to SP astrocytes. Ca^{2+} imaging of SP and SR astrocytes performed in acute slices revealed that SR astrocyte Ca^{2+} events had a greater frequency and temporal density, but reduced amplitude, relative to SP astrocytes, suggesting astrocyte Ca^{2+} signaling heterogeneity. Using the territorial segregation of Somatostatin (dendritic) and Parvalbumin (peri-somatic) inhibitory synapses, we observed that the selective activation using DREADD or blockade with intracellular BAPTA of the two populations of astrocytes regulated inhibitory synapses exclusively in their own syncytial territory. Furthermore, each astrocyte population selectively mediated long-term depression at the respective inhibitory synapses through Ca^{2+}-dependent modulation of post-synaptic targets. These results indicate a domain-specific regulation of inhibitory synapses by distinct SP and SR astrocyte syncytia. Overall, our findings reveal a functional specialization of astrocyte subtypes in the hippocampus, highlighting heterogeneous astrocyte regulation of hippocampal synaptic networks important for learning and memory.

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Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.10/B13

Topic: B.09. Glial Mechanisms

Title: Glia limitans expresses fibrinogen chains.

Authors: *E. GOLANOV, A. S. REGNIER-GOLANOV, N. KVIRKVELIA, H. CHUONG, N. HASSAN, R. CHANDRASEKARAN, G. W. BRITZ;
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Abstract: Cerebrospinal fluid (CSF) plays critical roles in the maintenance of normal brain function. While circulating along the subarachnoid space (SAS), the perivascular space, and through the brain parenchyma CSF removes byproducts of brain. Mechanisms of CSF flow regulation are not completely understood. The SAS and the perivascular space are separated from the brain parenchyma by a layer of astroglial endfeet known as *glia limitans*. As we and others demonstrated, subarachnoid hemorrhage (SAH) stalls the CSF flow for up to 3 weeks. Block of CSF can be reversed by blocking coagulation cascade member tissue factor known to be expressed by astrocyte. Moreover, SAH is accompanied by deposition of FBG/FBG chains along cerebral vessels. We speculate that FBG/FBG chains deposition hinders the flow of CSF to minimize harmful post-SAH bleeding. Based on our own preliminary experiments and published data we hypothesize that the astrocytic *glia limitans* is capable of expressing FBG and/or FBG-chains, which, in turn are capable of changing CSF conveyance along the SAS and the perivascular space. In naïve animals using immunohistochemistry we observed FBG gamma chain associated with AQP-4 suggesting colocalization of FBG gamma chain and astrocytic *glia limitans* endfeet, which is in agreement with observations by Stokum et al., 2021. Intra *cisterna magna* injection of kaolin significantly increased deposition of FBG along the cerebral vessel. To ascertain the intrinsic to endfeet origin of FBG gamma chain we employed RNA scope technology to detect presence of FBG gamma chain mRNA. After separation of microvessels from naïve mice brain and establishing attachment of endfeet to the outer segment of microvessels we were able to confirm presence of FBG gamma chain mRNA in the outer layer of microvessels coinciding with endfeet labeled with AQP-4. Based on these data we conclude that astrocytic endfeet are capable of expressing the FBG gamma chain, which can be amplified by proinflammatory signals.

Disclosures: E. Golanov: None. **A.S. Regnier-Golanov:** None. **N. Kvirkvelia:** None. **H. Chuong:** None. **N. Hassan:** None. **R. Chandrasekaran:** None. **G.W. Britz:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.11/B14

Topic: B.09. Glial Mechanisms

Support: Conahcyt I-935 Mexico

Title: Estradiol-dependent GLAST/EAAT1 Regulation in cerebellar Bergmann glia cells

Authors: *L. HERNANDEZ[1], E. CALDERON-ARANDA[2], A. G. RODRIGUEZ-CAMPUZANO[3], A. ORTEGA[2], F. CASTELÁN[4];
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Abstract: Glutamate is the major excitatory neurotransmitter within the Central Nervous System (CNS). The efficient removal of this amino acid from the synaptic cleft is crucial both for a correct signaling but also to prevent excitotoxic events. In the cerebellum. Bergmann glial cells due to their physiological and anatomical positioning play an important role in cerebellar plasticity such as long-term depression. Therefore, it is not surprising that Glutamate transporters' plasma membrane expression and function are tightly regulated at the transcriptional, translational, and post-translational levels. Among the neuroactive molecules present in the cerebellar cortex, estrogens have gained attention since, it has been demonstrated that 17-β estradiol is locally synthetized in Purkinje and granular cells. Using the well-characterized culture of chick cerebellar Bergmann glia cells, we report here a time and dose dependent increase in glutamate uptake activity, a detected *via* a [^{3}H] D-aspartate assay. Pharmacological experiments suggested that the 17-β estradiol effect is mediated through estrogen receptor α and GPR30 receptors. Taking into consideration that Bergmann glia cells express exclusively GLAST/EAAT1 transporters, our results provide an insight into the molecular transactions by which estrogens elicit its reported neuroprotective effects: an increase in the number and thus activity of plasma membrane glutamate transporters.

Disclosures: L. Hernandez: None. **E. Calderon-Aranda:** None. **A.G. Rodriguez-campuzano:** None. **A. Ortega:** None. **F. Castelán:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.12/B15

Topic: B.09. Glial Mechanisms

Support: CONAHCYT I-935 AO

Title: Glutamate-dependent Dynamic DNA Methylation in Müller cells: Mechanisms and Involvement in Excitotoxicity

Authors: *B. OYETAYO[1], L. C. HERNANDEZ[2], E. CALDERON-ARANDA[3], A. G. RODRIGUEZ-CAMPUZANO[4], F. CASTELÁN[5], A. ORTEGA[6];
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[5]Inst. de Investigaciones Biomedicas, UNAM, Tlaxcala, Mexico; [6]Toxicology, Cinvestav-IPN, Mexico City, Mexico

Abstract: Glutamate serves as the primary excitatory neurotransmitter within the Central Nervous System (CNS). Efficient removal of neuroactive glutamate from the synaptic cleft is crucial for maintaining extracellular concentrations below neurotoxic levels. Müller glial cells due to their physiological and anatomical positioning play a pivotal role in retinal ganglion cells' protection through the uptake of glutamate. Glutamate transporters' expression is tightly regulated at the transcriptional and translational levels for short and prolonged periods. Glutamate receptors expressed on glial membranes have been reported to induce changes in gene expression, upon stimulation. In neurons, dynamic DNA methylation, a form of transcriptional regulation and its role in regulating gene expression has been extensively studied. Using the cultured radial glia cells, studies from our laboratory and many others have also shown that this process is mediated by the activation of the AMPA subtype of glutamate receptors through a Ca2+/diacylglycerol-dependent Protein Kinase C/Ying Yang 1 signaling pathway. Recently, our group demonstrated an increase in 5-methylcytosine (5-mc) due to glutamate exposure and modulation in the expression and uptake activity of excitatory amino acid transporters 1 and 2 in primary cultures of chick-derived cerebellar Bergmann glia and a human-retinal Müller glia cell line under hypomethylating conditions. In this contribution, using the well-established model of retinal Müller glia primary cell culture, we explored the signaling cascades involved in glutamate receptor activation-induced changes in global 5-mc levels. The effect of the activation of AMPA and NMDA glutamate receptor subtypes on glutamate transporter activity and global DNA methylation is evident. In conclusion, our results provide further insights into the specific glutamate receptor subtype(s) and signal transduction pathways involved in dynamic DNA methylation and its role in glial cells' main function- glutamate clearance.

Disclosures: B. Oyetayo: None. **L.C. Hernandez:** None. **E. Calderon-Aranda:** None. **A.G. Rodriguez-campuzano:** None. **F. Castelán:** None. **A. Ortega:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.13/B16

Topic: B.09. Glial Mechanisms

Title: Effect of glyphosate on astrocyte-neuron communication: the role of extracellular vesicles.

Authors: *D. COMAI[1], A. GURGONE[1], V. CARDINALE[1], A. BATTAGLIA[2], L. MUNARON[3], G. TOMAGRA[2], V. CARABELLI[2], L. LEGGIO[4], N. IRACI[4], M. ZIBETTI[1,5], M. GIUSTETTO[1];
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Abstract: The widespread use of herbicides, including glyphosate (Gly), poses potentially underestimated risks to human health because their mechanism of action is not fully understood. Gly produces neurotoxic effects in mice, e.g. decrease in locomotor activity, increase in anxiety/depression-like behavior, and impairments in learning and memory. These signs are associated with neuronal and synaptic abnormalities, glutamatergic excitotoxicity, oxidative stress and increased levels of pro-inflammatory cytokines. Although Gly can cross the blood-brain barrier and penetrate the parenchyma, whether its effects may spread through alternative routes (e.g.: cell-to-cell communication) is unknown. Because astrocytes establish bidirectional contacts with vascular compartments and brain parenchyma, we hypothesize that Gly infiltration may firstly affect these cells and influence neuronal homeostasis by modifying astrocyte-neuron communication. To test this idea, we used primary astrocytic cultures derived from the cerebral cortex of early postnatal mice that were analyzed using biochemistry, morphology and electrophysiology. First, we assessed that treating these cultures for 24 hours to increasing concentrations of subtoxic doses of Gly does not modify cell viability. Interestingly, the exposure to 3μM Gly, a concentration aligned with the acceptable daily intake dose (European Food Safety Authority), induced notable changes in astrocytic morphology, GFAP expression, associated with increased release of astrocyte-derived extracellular vesicles (ADEVs). ADEVs are nanoscale vesicles enclosed by a lipid bilayer containing a pool of molecules (e.g.: miRNAs, proteins, lipids) which functions include neural circuits regulation. To functionally assess ADEVs isolated from Gly-treated astrocytes, we added physiological concentrations of ADEVs ($1x10^9$ ADEVs/mL) to cortical neuronal cultures and assessed both neuronal and synaptic integrity after 24 hours. Gly-ADEVs caused a significant reduction of both dendritic complexity and excitatory synapses density as revealed by immunofluorescence and high-resolution confocal microscopy. Experiments assessing Gly-ADEVs impact on synaptic transmission and synchronization are ongoing to clarify the molecular mechanisms underlying their effects. In sum, these findings indicate that Gly, by affecting ADEVs production and release, may interfere with astrocyte-neuron communication, at least in-vitro, to generate neurotoxicity and synaptic dysfunction.

Disclosures: D. Comai: None. **A. Gurgone:** None. **V. Cardinale:** None. **A. Battaglia:** None. **L. Munaron:** None. **G. Tomagra:** None. **V. Carabelli:** None. **L. Leggio:** None. **N. Iraci:** None. **M. Zibetti:** None. **M. Giustetto:** None.

Poster

PSTR104: Astrocyte Cell Biology

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Program #/Poster #: PSTR104.14/B17

Topic: B.09. Glial Mechanisms

Title: Insulin signaling in astrocytes entrain circadian rhythms via dopamine signaling

Authors: *A. GONZÁLEZ VILA[1,5], M. LUENGO MATEOS[2], M. SILVEIRA LOUREIRO[2,5], P. GARRIDO-GIL[3], M. GONZÁLEZ DOMÍNGUEZ[2], A. MOHAMMAD ALASOUFI[7,8], J. L.

LABANDEIRA-GARCIA[4], C. GARCIA-CACERES[9], M. LÓPEZ[6], O. BARCA-MAYO[2]; [2]Circadian and Glial Biol. Lab, Physiol. Dept., [3]Cell and Mol. Neurobio. f Parkinson disease, [1]Singular Ctr. for Res. in Mol. Med. and Chronic Dis., Santiago de Compostela, Spain; [4]Cell and Mol. Neurobio. f Parkinson disease, Singular Ctr. for Res. in Mol. Med. and Chronic Dis., Santiago Compostela, Spain; [5]NeurObesity Lab, Physiol. Department, Mol. Medicine, and Chronic Dis. Res. Ctr. (CiMUS), Univ. of Santiago de Compostela, Santiago de Compostela, Spain; [6]NeurObesity Lab, Physiol. Department, Mol. Medicine, and Chronic Dis. Res. Ctr. (CiMUS), Univ. of Santiago de Compostela, Santiago De Compostela, Spain; [7]Biology, Alhussein Bin Talal Univ., Maan, Jordan; [8]Physiol. Dept., Circadian and Glial Biol. Lab, Physiol. Department, Mol. Medicine, and Chronic Dis. Res. Ctr. (CiMUS), Univ. of Santiago de Compostela, Santiago de Compostela, Spain; [9]Helmholtz Zentrum München & German Ctr. for Diabetes Res. (DZD), Munich, Germany

Abstract: In mammals, endogenous circadian clocks sense and respond to daily feeding and lighting cues, adjusting internal ~24-hour rhythms to resonate with and anticipate external cycles of day and night. This timing system consists of a central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks in tissues or organs throughout the body. The mechanism underlying circadian entrainment to feeding time is critical for understanding why mistimed feeding, as it occurs, for example, during shift work, disrupts circadian physiology, associated with increased chronic diseases such as type 2 diabetes. Notably, feeding-regulated hormone insulin (INS) resets peripheral clocks in vivo and in vitro. Conversely, mistimed INS signaling disrupts the circadian organization of clock gene expression and mice behavior. Recent findings have shown the critical role of the astrocytic clock in regulating daily rhythms in physiology and behavior.To uncover the role of the insulin receptor (IR) in astrocytes, we used a Cre/lox approach to genetically delete IR exclusively from GLAST-positive astrocytes. We show that astrocytic INS signaling sets the free-running period of locomotor activity in female mice and food entrainment in male mice. Additionally, ablating the IR in hypothalamic astrocytes alters cyclic energy homeostasis differently between male and female mice. Remarkably, the mutants exhibit altered dopamine metabolism. Moreover, the pharmacological modulation of dopaminergic signaling, when we administer a D2 receptor agonist, partially restores distinct circadian traits in both male and female mutant mice. Our findings highlight the role of astrocytic INS-dopaminergic signaling in conveying time-of-feeding or lighting cues to the astrocyte clock, thus governing circadian behavior in a sex-specific manner.

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Poster

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Program #/Poster #: PSTR104.15/B18

Topic: B.09. Glial Mechanisms

Title: Lrp4+ astrocytes represent a unique subtype of astrocyte that are critical for suppressing gliosis and maintaining vasculature in the cortex

Authors: *E. ARZOLA[1], W.-C. XIONG[2];
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Abstract: Low density lipoprotein receptor type 4 (LRP4) is a transmembrane receptor that binds various ligands, including SOST and Agrin, and is a critical regulator of bone density and NMJ innervation/maintenance, respectively. Previously, our lab has shown that LRP4 is also expressed in astrocytes in the brain and regulates ATP release, presynaptic glutamate release, and sEPSC frequency. Interestingly, LRP4 is expressed in a small subset of cortical astrocytes with dense concentration along the top layer near the meninges. Surprisingly, LRP4+ astrocytes do not express GFAP, but do express GLAST1, suggesting these cells may be unique from other cortical astrocytes. To study the function of this sub-population, I induced the ablation of LRP4+ astrocytes *in vivo* via diptheria toxin, resulted in severe increase of GFAP+ astrocytes and activated microglia, reduced pericyte coverage, reduced blood vessel diameter, and reduced cerebral blood flow. Surprisingly, the ablation of GFAP+ astrocytes did not recapitulate this phenotype. LRP4 has been linked to AD, as it serves as a receptor for ApoE2-4 and APP. We've previously shown that LRP4 is decreased in the cortex and hippocampus of AD patients, and the loss of LRP4 in astrocytes in 5xFAD mice results in increased Aβ plaques and worsened cognitive impairment. Moreover, in 5xFAD mice, loss of LRP4+ astrocytes resulted in increased Aβ plaque size and density, and decreased GFAP+ astrocyte-Aβ plaque interaction. Lastly, LRP4+ astrocytes do not upregulate GFAP and tend to avoid interacting with amyloid plaques, adding to the unique characteristics of these cells. Together, this study reveals that LRP4+ astrocytes may represent a unique cortical astrocyte sub-type that demonstrates anti-inflammatory properties and plays a critical role in blood vessel maintenance and Aβ clearance.

Disclosures: E. Arzola: None. **W. Xiong:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.16/B19

Topic: B.09. Glial Mechanisms

Support: CIHR
NSERC

Title: G-protein mediated regulation of glial activation and TNF production

Authors: *Z. ABBASI[1], D. STELLWAGEN[2];
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Abstract: Neuromodulators generally act through G-protein-coupled receptors, but their effects on glia are not well defined. Here we examine the impact of various G-protein-coupled receptors on glia, using the production of the pro-inflammatory cytokine Tumor necrosis factor alpha (TNF) as a measure of activation. TNF is a major part of the innate immune response but is also an important regulator of synaptic function and can be released by both astrocytes and microglia. We characterized the response to activation of the Gi, Gq, and Gs signaling pathways. Through a series of experiments involving Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)-based and pharmacological approaches in rat astrocyte and microglia cultures and human induced pluripotent stem cells (hiPSCs) derived astrocytes, our findings showed distinct actions of different G protein pathways. Activation of Gs-GPCRs results in a decrease in TNF expression in both types of glial cells. Similarly, activation of Gq pathways also results in a reduction in TNF mRNA levels. Conversely, Gi activation in astrocytes and microglia increases TNF levels. This is reversed from the activation or inhibition seen in neurons to these same G-protein cascades. Overall, this work demonstrates that G protein-mediated activation and inhibition in glia should be considered separately from the effects seen in neurons.

Disclosures: Z. Abbasi: None. **D. Stellwagen:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.17/B20

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5KA01DA054449

Title: A comparison of astrocyte organization across brain regions and species

Authors: *A. GREY[1], T. BAKKEN[2], R. D. HODGE[3], Y. GODA[4], H. NEDELESCU[5], S. SRINIVASAN[6];
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Abstract: Astrocytes are integral to synaptic transmission and plasticity, and ultimately, brain function. Their morphology differs from other cells including neurons. Indeed, morphologies even vary between brain regions and species. The reason for their shape and especially variatons is less well understood. Understanding the basis for their particular morphology is crucial to know how they connect and influence surrounding cells such as neurons, and regulate circuit function. To link morphology and circuit function, we quantitatively characterized astrocyte organization in several species and brain regions. We found that astrocyte densities were

conserved within somatosensory cortices of cats and rabbits, and piriform cortices of mice and primates, while varying between them. To test if morphologies, too, exhibit a similar trend, we traced and compared astrocyte morphologies in the mouse hippocampus (GFP-filled) and in EM datasets from mouse V1 and human temporal cortex. These findings, together with the finding of conserved astrocyte densities can help in developing a model of astrocyte organization showing how evolution fine tunes astrocytes to suit circuit-specific demands.

Disclosures: A. Grey: None. **T. Bakken:** None. **R.D. Hodge:** None. **Y. Goda:** None. **H. Nedelescu:** None. **S. Srinivasan:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.18/B21

Topic: B.09. Glial Mechanisms

Support: PAPIIT-UNAM IN202922
CONAHCyT 2021-00018-02NACF-19488, CVU 859848

Title: Effect of D-beta-hydroxybutyrate on autophagy dynamics in cultured astrocytes

Authors: *P. CORONADO[1], L. MASSIEU[2], T. MONTIEL[3];
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Abstract: Effect of D-beta-hydroxybutyrate on autophagy dynamics in cultured astrocytes
Authors*P. CORONADO, T. MONTIEL, L. MASSIEU; Departamento de Neuropatología Molecular, División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Ciudad de México, México.
DisclosuresP. Coronado: None. **T. Montiel**: None. **L. Massieu**: None.
β-hydroxybutyrate (BHB) is a ketone body (KB) that has been proposed for treating acute cerebral injury and neurodegenerative diseases. Several studies, in in vivo and in vitro models, have shown that BHB enhances neuronal viability through different mechanisms including the stimulation of autophagy. In neurons, BHB can promote the activity of the transcription factors TFEB, FOXO1 and FOXO3a, which regulate autophagy, lysosomal biogenesis and mitophagy, conferring resistance to glucose deprivation. In addition to neurons, astrocytes can transport and metabolize KB, but it is unknown to what extent the protective effect of BHB in vivo is mediated by its action in neurons and/or astrocytes. Besides, the effect of BHB on autophagy in astrocytes has not been elucidated. Therefore, the aim of this study is to investigate the effect of BHB on autophagy dynamics in astrocyte cultures under basal conditions and oxygen and glucose deprivation (OGD), and its relationship to cell survival. Using western blot and immunofluorescence assays, we determined that BHB incubation during 6-48 h stimulates the

basal autophagic flux, as there is an increase in the levels of the LC3-II and a decrease in p62 protein content, accompanied by an increase in the number of autophagosomes. BHB also increased AMPK phosphorylation, indicative of autophagy initiation. Furthermore, exposure to BHB leads to an increase in TFEB protein levels in both the nucleus and cytoplasm, and its phosphorylation decreases suggesting its activation. In addition, the content of lysosomal protein, LAMP1, increases. These findings suggest that TFEB may play a role in activating the expression of autophagy-lysosomal genes. BHB treatment preserves the viability of astrocytes subjected to oxygen-glucose deprivation (OGD). In conclusion, our results indicate that BHB exposure stimulates the autophagy-lysosomal axis in healthy astrocytes, rendering them less vulnerable to OGD.This work was supported by PAPIIT-UNAM IN202922 grant to LM, and CONAHCyT 2021-00018-02NACF-19488.

Disclosures: P. Coronado: None. **L. Massieu:** None. **T. Montiel:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.19/B22

Topic: B.09. Glial Mechanisms

Support: EU-Horizon MSCA-ASTROTECH-956325
AFOSR-FA9550-20-1-0386
AFOSR-FA9550-23-1-0736

Title: Effect of 40 Hz Light on Calcium Dynamics of Astrocytes

Authors: *A. KONSTANTOULAKI[1,2], M. HORNING[3,4], T. EGHOLM RUDE[4], R. FABBRI[1], C. LAZZARINI[1], G. CONTE[1], D. SPENNATO[1], M. CAPRINI[5], M. SCHULTZ CARSTENSEN[4], V. BENFENATI[1];
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Abstract: Recent studies suggest that gamma entrainment may have beneficial effects in patients with Alzheimer's Disease (AD). The neuroprotective effect of gamma stimulation could be driven by different cell types, including astrocytes, yet the underlying mechanisms remain unclear. Astrocytes communicate mainly through Ca^{2+} signalling, the dysfunction of which, is linked to compromised synaptic activity, network impairments and neurological pathologies such as AD. Based on this premise, employing live fluorescent imaging and pharmacology, we investigate the effect of 40 Hz optical stimulation on primary neonatal rat astrocytes' calcium signalling and ion channels' functions. To administer gamma stimulation, a customised version of OptoCeutics' novel light therapy system (LTS; Optoceutics ApS, Copenhagen, Denmark) was used. LTS is a light-based neurostimulation device which employs a novel technology utilising

an Invisible Spectrum Flicker (ISF) at 40 Hz with alternating colour schemes, currently tested in clinical trials as a potential treatment for AD. As a control, continuous white light of the same properties is used (PLACEBO). Our findings suggest that astrocytic function could be modulated by 40 Hz ISF light, as we detect alterations in Ca^{2+} signalling. Using selective pharmacology, we explore the precise underlying mechanisms elucidating the involvement of intracellular Ca^{2+} release and extracellular Ca^{2+} influx in the response. We found that light stimulation induces Ca^{2+} signalling and the observed response is dependent on the frequency of light. The percentage of responding cells is significantly higher after both ISF and PLACEBO stimulation. In the case of ISF, extracellular Ca^{2+} appears to be important for the magnitude of the response and not for the dynamics while in the case of PLACEBO, extracellular Ca^{2+} plays a role also on the dynamics of the response. In addition, ISF light stimulation induces an earlier response with respect to PLACEBO. Thus, we hypothesise that the two stimuli recruit different Ca^{2+} pathways, possibly due to differences in light frequency. Cumulatively, the results presented indicate that 40 Hz ISF is a consistent method to precisely elicit intracellular calcium signalling in astrocytes, without affecting cell viability or causing phototoxicity, and shine further insight into how different properties of light might be used to affect or perturbate astrocytes' calcium signalling.

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Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.20/B23

Topic: B.09. Glial Mechanisms

Support: AFOSR-FA9550-23-1-0736
AFOSR-FA9550-20-1-0386
EU-Horizon MSCA-ASTROTECH-956325

Title: Nanostructured Zirconia Surfaces Promote Neurogliomorphic Interactions in Glial and Neuronal Cultures

Authors: *G. CONTE[1], C. LAZZARINI[2], F. BORGHI[3], A. KONSTANTOULAKI[4], R. FABBRI[5], M. CAPRINI[6], P. MILANI[7], V. BENFENATI[8];
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Abstract: Neuromorphic materials and devices have recently garnered attention for their potential in developing efficient neuromorphic computing systems that can emulate the functions of neuronal synapses. However, in the real nervous system, the synapse involves at least a three-element unit where glial cells play a critical role in tuning synaptic efficiency. Our vision is to expand beyond the neurocentric perspective of neuromorphic computing by including glia as an essential element of artificial synapses, akin to their role in vivo. To advance this long-term goal, we investigated the impact of neuromorphic materials[1,2] on astrocytes and neurons from the central and peripheral nervous systems. Specifically, we cultured primary rat neocortical astrocytes, Dorsal Root Ganglion (DRG) neurons, and Satellite Glia (SG) co-cultures on nanostructured zirconia surfaces produced through supersonic cluster beam deposition of zirconia nanoparticles. Our study aimed to evaluate biocompatibility, molecular and functional profiles through various assays including cell viability assessments, immunofluorescence and confocal microscopy, RT-qPCR, and calcium imaging. Our findings demonstrate that nanostructured zirconia surfaces promote the differentiation of primary glial cultures. Primary cortical astrocytes cultured on these surfaces exhibited enhanced differentiation, with earlier activation of astrocyte calcium dynamics compared to flat control surfaces. Pharmacological analysis revealed involvement of intracellular calcium release, extracellular calcium influx, and gap junctional hemichannels in the observed calcium dynamics, as indicated by calcium imaging and RT-qPCR showing differences in ion channel transcription levels on nanostructured zirconia substrates compared with flat substrates. Furthermore, DRG neurons adhered and grew more orderly networks on zirconia nanostructured substrates, with distinct calcium signaling patterns and pharmacological responses observed in both neuronal and glial cells. Immunofluorescence analysis confirmed the expression of specific neuronal (GAP-43) and glial markers (Cx-43) on zirconia nanostructured surfaces without the need for additional coating. Collectively, our study establishes nanostructured zirconia as a neurogliomorphic material, suggesting that the signaling interactions at the cell-material interface could be harnessed to explore novel brain-computer interfaces and neuromorphic computing approaches[3].[1]doi: 10.1021/acsbiomaterials.8b00916[2] doi: 10.3390/cells12020293[3] doi: 10.1088/1361-6463/acd704 *GC, CL, FB contributed equally

Disclosures: G. Conte: None. **C. Lazzarini:** None. **F. Borghi:** None. **A. Konstantoulaki:** None. **R. Fabbri:** None. **M. Caprini:** None. **P. Milani:** None. **V. Benfenati:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.21/B24

Topic: B.09. Glial Mechanisms

Support: NSF NN1 award 1707356
NSF NN2 2014862
NIH award 5R01MH095980-09

Title: Astrocytic processes remain closely associated with >80% of excitatory synapses during synaptic plasticity in the hippocampal dentate gyrus

Authors: *A. J. NAM[1,2], M. KUWAJIMA[2], J. M. MENDENHALL[2], P. PARKER[2], D. HUBBARD[2], W. C. ABRAHAM[3], K. M. HARRIS[1,2];
[1]Inst. for Neurosci., Univ. of Texas at Austin, Austin, TX; [2]Ctr. for Learning & Memory, Univ. of Texas At Austin, Austin, TX; [3]Dept. of Psychology, Univ. of Otago, Dunedin, New Zealand

Abstract: Astrocytes are intimately involved in vital synaptic processes. Astrocytic processes interdigitate the dense neuropil of dendritic spines and axons where they influence information processing. We investigate the ultrastructural relationships between astrocytic processes and synapses to assess their capacity to have unique functional roles in disparate brain regions and synaptic plasticity. Here we leverage 3D reconstruction from serial section electron microscopy to investigate astrocytic relationships to synapses across axonal inputs undergoing different forms of synaptic plasticity in the hippocampal dentate gyrus. Long-term potentiation (LTP) and concurrent long-term depression (cLTD) are widely accepted cellular mechanisms of learning and memory. Delta-burst stimulation delivered to the medial perforant pathway of adult rats produced LTP in the middle molecular layer. In parallel, cLTD occurred in the outer molecular layer. The contralateral hemispheres of each animal received only test pulses at baseline levels in the medial path, and thus served as within-subject controls. An automated pipeline using the computer graphics software, Blender, was developed to measure astrocyte coverage around reconstructed synapses. In all layers and conditions, more than 85% of synapses had a close association with astrocytic processes located within 0.1 µm of the axon-spine interface (ASI). The degree to which astrocytic processes surround the ASI scaled linearly with the total length of the ASI perimeter, but reached full coverage at <1% of synapses. The astrocytic processes maintained this close relationship with dentate granule cell synapses during LTP, contrasting with hippocampal area CA1 synapses where prior studies have shown that astrocytic processes retract during LTP. At 30 minutes after the induction of cLTD in the outer molecular layer the fraction of synapses with astrocytic processes at the axon-spine interface decreased approximately 7%, suggesting cLTD might be associated with astrocyte retraction. The results highlight the diversity of relationships between astrocytic processes and synapses across brain regions and functions. The outcomes are consistent with dentate gyrus synapses requiring a robust astrocytic infrastructure to support pattern separation and other functions unique to this brain region.

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Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.22/B25

Topic: B.09. Glial Mechanisms

Support: NIH CNAP COBRE Grant P20GM113109

Title: Internalization of human astrocyte exosomes by neighboring cells

Authors: *M. KUMARI;
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Abstract: Title: Internalization of astrocytic exosomes by neighboring cells**Name and affiliation**: Meena Kumari, Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506**Conflict of Interest**: None**Abstract**: Astrocytes, the most abundant type of glial cell in the brain, perform several important functions through 1) direct contact and 2) release of soluble factors including neurotransmitters, metabolites, and growth factors. In addition, they release exosomes that originate in multivesicular bodies and contain macromolecules, some of which are unique. Internalization of exosomes by recipient cells can modulate their gene expression thereby influencing their physiology and, in some cases, morphology of recipient cells. Our goal is to understand the impact of astrocytic exosomes on neighboring cells. In the present study, we optimized culture conditions of commercially purchased human astrocytes and confirmed their identity by examining expression of GFAP, vimentin, glutamine synthetase, and CD49f by Western blotting and immunocytochemistry. Astrocytic exosomes purified by ultracentrifugation method had an average mode size of 128 nm (nanosight analysis). Cultured astrocytes released 8.03e+08 exosomes per day per mL of conditioned medium. Transmission electron microscopy confirmed exosome ultrastructure and cryo-electron microscopy confirmed lipid bilayers of exosomes with electron dense internal structure. After confirming that Dil-labeling did not alter size of exosomes, Dil-labeled astrocytic exosomes were incubated with astrocytes and neurons to examine their internalization. Both neurons and astrocytes internalized astrocytic exosomes but at different rate. Currently, we are examining how internalized exosomes impact recipient cells. **Acknowledgement**: Research reported in this abstract was supported partially by the Cognitive and Neurobiological Approaches to Plasticity (CNAP) Center of Biomedical Research Excellence (COBRE) of the National Institutes of Health under grant number P20GM113109. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures: M. Kumari: None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.23/B26

Topic: B.09. Glial Mechanisms

Support: BBRF Young Investigator Grant
Owens Family Foundation

Title: Hippocampal CA2 perineuronal net sulfation is associated with astrocyte dysregulation

Authors: *P. KRASZEWSKI, S. HASHMI, S. LEE, E. C. COPE;
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Abstract: The hippocampal CA2, an area characterized as a “hub” for social memory circuitry, has a high abundance of perineuronal nets (PNNs) - specialized extracellular matrix structures that regulate brain plasticity. BTBR mice, a model of social memory dysfunction, display increased CA2 PNNs; reducing PNNs to control-like levels improves social memory. Here, we show that excess PNNs in BTBR mice coincides with a shift in astrocyte populations, where GFAP+ astrocytes are selectively diminished with no change in total astrocyte number. Reducing PNNs in BTBR mice rescues GFAP+ astrocyte expression, suggesting a link between excessive PNNs and astrocytic function. One possibility is that PNN composition impacts astrocytic plasticity. One of the key PNN components, chondroitin sulfate proteoglycans, are sulfated mainly at the 4 (C4S) and 6 (C6S) positions, which have differing effects on PNN plasticity. We observed a marked increase in C6S intensity and a decrease in C4S intensity in the CA2 of BTBR mice. BTBR mice with reduced PNNs maintained high C6S levels, suggesting that C6S+ PNN abundance is not directly responsible for shifts in glial marker expression. Evidence suggests that astrocytes produce sulfotransferase enzymes, thus an alternate possibility is that dysregulated astrocytes in BTBR mice are responsible for excessive C6S+ PNNs. Since calcium signaling plays a major role in regulating astrocytic function, we virally inhibited intracellular astrocytic calcium in control mice using calcium extruder (“CalEx”) expression. We found an increase in C6S, but not C4S, deposition onto CA2 PNNs in CalEx virus-infected mice. Yet, depletion of microglia with colony stimulating factor 1 receptor inhibitor had no effect on CA2 PNN sulfation patterns. These data suggest that astrocytic calcium regulates C6S PNN-associated sulfation patterns, although its role and effects on social memory function remains unknown.

Disclosures: P. Kraszewski: None. **S. Hashmi:** None. **S. Lee:** None. **E.C. Cope:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

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Program #/Poster #: PSTR104.24/B27

Topic: B.09. Glial Mechanisms

Support: FONDECYT 3230595 (ER)
FONDECYT 1240486 (KS)
FONDECYT 1221147 (FN)
CMA BIO-BIO PIA-ANID ECM-12 (FN)

Title: Age-related astrocytes impair vitamin C recycling in the brain

Authors: *E. RAMÍREZ[1], L. FERRADA[1], K. A. SALAZAR[2], F. A. MARTINEZ ACUÑA[3], R. MAGDALENA[1], S. ELGUETA[1], M. CABRERA AROS[1], F. J. NUALART[4];
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Abstract: Astrocytes are the main cells of glial origin in the adult brain that support metabolic and structural neuronal functions. Some antioxidants such as vitamin C are recycled between astrocytes and neurons to maintain antioxidant homeostasis. The reduced form, ascorbic acid (AA) is captured in neurons by the Sodium-dependent vitamin C transporter 2 (SVCT2). Whereas GLUT1, the transporter of the oxidized dehydroascorbic acid (DHA) is expressed by astrocytes. Interestingly, previous work in different pathological models shows that reactive astrocytes express SVCT2, suggesting impaired vitamin C recycling in the CNS. In terms of aging, this is unknown. Using the Senescence Accelerated Mouse Prone 8 (SAMP8) mice we analyzed astrocytic GFAP pattern in brain tissue at different ages (2-14 months) by immunohistochemistry (IHC) and CLARITY. We also studied the expression of SVCT2, KDEL, and GFAP in brain samples by spectral LSM780 Zeiss confocal microscopy and qRT-PCR after laser microdissection. In addition, we isolated astrocytes from postnatal mice (0-3 days), which were studied after 7 and 30 days in culture, and functional analyses of AA transport were performed, in the presence or absence of neuronal Neuro2a cells. IHC revealed high SVCT2 expression in neurons (KDEL+) at 2 months of age, and it is not observed in astrocytes. However, from 2 to 14 months, SVCT2 was preferentially detected in activated astrocytes (GFAP+), decreasing its detection in neurons from different brain areas. These changes were mainly found in the cerebral cortex and the cerebellum. In vitro, 7-day astrocytes do not take up AA and do not compete for AA with the Neuro2a cells. However, after 30 days astrocytes take up AA and reduce the entry of AA into Neuro2a cells. These data suggest that age-related astrocytes compete with neurons for AA, thus impairing the proper vitamin C recycling and leading to neurocognitive deterioration in the aging brain.

Disclosures: E. Ramírez: None. **L. Ferrada:** None. **K.A. Salazar:** None. **F.A. Martinez Acuña:** None. **R. Magdalena:** None. **S. Elgueta:** None. **M. cabrera aros:** None. **F.J. Nualart:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

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Program #/Poster #: PSTR104.25/B28

Topic: B.09. Glial Mechanisms

Support: NIH Grant R21NS121821

Title: Store Operated Calcium Entry in iPSC-derived Astrocytes

Authors: *E. BEREZOVSKI[1], J. T. SMYTH[2];
[1]Uniformed Services Univ., Bethesda, MD; [2]Anat. & Physiol., Uniformed Services Univ., Bethesda, MD

Abstract: Astrocytes contribute to synaptic function through replenishing pre-synaptic neurotrasmitters by release of precursor molecules, and through release of active neurotrasmitters in a process called gliotransmission. These processes of the tripartite synapse depend on complex and poorly defined calcium signaling mechanisms in astrocytes. A role for the specific calcium signaling process known as store-operated calcium entry (SOCE) has been demonstrated in astrocytes from various animal models including mice and flies but SOCE function has never been tested in human astrocytes. This is important because astrocytes between species vary greatly in their morphology and calcium signaling processes. SOCE is activated in response to depletion of endoplasmic reticulum (ER) calcium stores, and involves the formation of complexes between ER-localized calcium sensitive STIM proteins and plasma membrane calcium-selective Orai channels. Calcium that enters the cell through Orai channels can directly activate signaling processes including gliotransmitter exocytosis and gene expression changes, as well as replenish depleted ER calcium stores. We have utilized induced pluripotent stem cell (iPSC)-derived astrocytes to test SOCE function in human astrocytes. The human genome encodes two STIM and three Orai variants (STIM1 and 2, and Orai1-3, respectively, and quantitative reverse-transcriptase PCR (qRT-PCR) demonstrates that iPSC-derived human astrocytes primarily express Orai1, Orai3, and STIM1 transcripts. Direct measurement of SOCE in iPSC astrocytes using fura-2 calcium imaging and thapsigargin-mediated depletion of ER calcium stores showed robust SOCE-mediated calcium influx, and this store depletion-induced calcium influx was blocked by the SOCE-specific inhibitors Synta66 and SKF-96365. We are currently combining siRNA-mediated knockdown of specific STIM and Orai isoform expression with direct SOCE measurements to determine the specific molecular composition of the SOCE machinery in human astrocytes, with the ultimate goal of testing the role of astrocyte SOCE in synaptic regulation in human astrocyte and neuron co-cultures.

Disclosures: E. Berezovski: A. Employment/Salary (full or part-time):; Henry Jackson Foundation. **J.T. Smyth:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.26/B29

Topic: B.09. Glial Mechanisms

Title: Connectomic analysis of astrocyte-synapse interactions in mouse cortex

Authors: *Y. YENER[1], A. MOTTA[2], M. HELMSTAEDTER[3];
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Abstract: While astrocytes are well established as providing metabolic support to neurons, their possible role as a synaptic partner has also been considered, giving rise to the notion of "tripartite" synapses, and suggesting a contribution to neuronal computations. For astrocytes to serve such purposes, the interactions with synapses in neuronal circuits require a level of specificity beyond overall synaptic support. A systematic mapping of the astrocyte-connectome interaction is however still lacking, in particular for circuits in the cerebral cortex. Here, analyzing previously published connectomic data from the layer 4 of the somatosensory cortex for the glia-synaptic interaction of more than 200,000 synapses, we systematically analyzed the spatial relation between astrocytes and synapses in mouse cortex. We developed a quantitative assessment of glia-synapse proximity, finding that only 22.7% of synapses are contacted by astrocytic processes for more than 50% of their synaptic circumference, rendering astrocytic-synaptic specificity plausible. We then observed a strong dependence of astrocytic synaptic coverage on synapse size, which was exclusive for excitatory spine synapses. Glial coverage depended on connectomic synapse types, with thalamocortical shaft synapses being almost completely embedded in astrocytic processes. We then investigated the possible relation of synaptic coverage to neuronal activity and synaptic plasticity, finding evidence for astrocytic withdrawal for possible long-term depression states, but no strong evidence for relation to overall neuronal presynaptic activity. Together, our data demonstrate a surprising level of specificity for particular synaptic types and indicate the relevance of astrocytic coverage for synapse stability, in particular for large synapses, suggesting an involvement in long-term maintenance of learned synaptic states. We are now exploring similar analyses in other layers of the cortex.

Disclosures: Y. Yener: None. **A. Motta:** None. **M. Helmstaedter:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.27/B30

Topic: B.09. Glial Mechanisms

Support: PID2021-122586NB-I00
RTI2018-094887-B-I00
R01NS097312
R01DA048822
F31AG057155
PRX19/00646
BFU2017-88393-P
R01MH119355
PID2019-105020GB-100
BA15/00078

Title: A spatial threshold for astrocyte calcium surge

Authors: *J. LINES[1], A. M. BARAIBAR[2], C. PEREZ DE NANCLARES[3], E. MARTIN[4], J. R. AGUILAR[5], P. KOFUJI[3], M. NAVARRETE[4], A. ARAQUE[3];
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Abstract: Astrocytes are active cells involved in brain function through the bidirectional communication with neurons, in which the astrocyte calcium signal plays a crucial role. Synaptically-evoked calcium increases can be localized to independent subcellular domains or expand to the entire cell, i.e., calcium surge. In turn, astrocytes may regulate individual synapses by calcium-dependent release of gliotransmitters. Because a single astrocyte may contact ~100,000 synapses, the control of the intracellular calcium signal propagation may have relevant consequences on brain function by regulating the spatial range of astrocyte neuromodulation of synapses. Yet, the properties governing the spatial dynamics of the astrocyte calcium signal remains poorly defined. Imaging subcellular responses of cortical astrocytes to sensory stimulation in mice, we show that sensory-evoked astrocyte calcium responses originated and remained localized in domains of the astrocytic arborization, but eventually propagated to the entire cell if a spatial threshold of >23% of the arborization being activated was surpassed. Using transgenic *$IP_3R2^{-/-}$* mice, we found that type-2 IP_3 receptors were necessary for the generation of the astrocyte calcium surge. We finally show using in situ electrophysiological recordings that the spatial threshold of the astrocyte calcium signal consequently determined the gliotransmitter release. Present results reveal a fundamental property of astrocyte calcium physiology, i.e., a spatial threshold for the astrocyte intracellular calcium signal propagation, which depends on astrocyte intrinsic properties and governs the astrocyte integration of local synaptic activity and the subsequent neuromodulation.

Disclosures: J. Lines: None. **A.M. Baraibar:** None. **C. Perez de Nanclares:** None. **E. Martin:** None. **J.R. Aguilar:** None. **P. Kofuji:** None. **M. Navarrete:** None. **A. Araque:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.28/Web Only

Topic: B.09. Glial Mechanisms

Support: CIHR Grant GR028432

Title: Neuroinflammatory activation of microglia drives piezo1 expression in astrocytes

Authors: *Y. BAI[1], H. CHOI[2], S. WENDT[3], M. TOWRISS[4], C. J. GROTEN[4], B. A. MACVICAR[5];
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Abstract: Numerous brain disorders are associated with mechanical alterations in the tissue microenvironment. Recent evidence indicates that such mechanical changes are sufficient to initiate mechanosensory signaling pathways and impact neuropathology. However, the precise mechanisms which regulate mechanosensory signaling in brain pathology remain uncertain. In our study, we addressed this by examining how the expression of astrocyte Piezo1, a mechanosensitive ion channel, is modulated by inflammatory triggers. To do this, we used rodent primary astrocyte and microglia cultures as our cell models. Using qPCR and Western blotting we found that either LPS or oligomer Aβ(oAβ) treatment of astrocyte cultures had either no effect or only very slight increases in piezo1 expression. However, when LPS or oAβ were added to microglia cultures, not only microglia piezo1 expression increased, the conditioned media from these microglia cultures significantly increased piezo1 expression in astrocytes. Additionally, we found that proinflammatory cytokines released by microglia after these treatment, contained interleukin 1α, interleukin 1β, and TNFα that alone can significantly increase Piezo1 expression in astrocytes. Collectively, our results suggest that upregulated Piezo1 expression in astrocytes is triggered indirectly, through microglia-dependent activation and cytokine release. This microglia-astrocyte cross talk may play a critical role in facilitating astrocyte mechanosensation and modulating the homeostatic functions of astrocytes.

Disclosures: Y. Bai: None. **H. Choi:** None. **S. Wendt:** None. **M. Towriss:** None. **C.J. Groten:** None. **B.A. MacVicar:** None.

Poster

PSTR104: Astrocyte Cell Biology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.29/B31

Topic: B.09. Glial Mechanisms

Support: U.S. Army MURI W911NF1910280
NIH U19 NS128613
NIH R01AT011439
NIH R01AT012312RF1AG057575

Title: Quantification of artery to vein cerebrospinal fluid transport via the glymphatic system

Authors: *M. J. GIANNETTO[1], M. NEDERGAARD[2];
[1]Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY; [2]Ctr. for Translational Neuromedicine, Univ. of Rochester, Rochester, NY

Abstract: The brain is highly metabolically active, producing high amounts of waste, yet lacks lymphatic vessels. Instead, waste is cleared via cerebrospinal fluid (CSF) circulation through the

glymphatic system, a network of perivascular spaces (PVSs) surrounding arteries and veins. These PVSs facilitate exchange of clean CSF from arteries to the brain parenchyma, which then clears waste to veinous PVSs and meningeal lymphatic vessels. Arterial CSF flow is well characterized, yet the clearance of CSF to veins has not been well quantified. To better understand this artery to parenchyma to vein directional flow, we utilized cisterna magna (CM) infusions of fluorescent tracer to label CSF. We infused 70kDa-TxRed dextran in the CM of NG2-dsRed transgenic mice and allowed circulation for 30 minutes or 120 minutes under ketamine/xylazine anesthesia to approximate sleep state (n=3 mice each group). Mice were then cardiac perfusion fixed with intravenous wheat germ agglutinin (WGA-647) to label all vasculature, then their brains sectioned and imaged with a fluorescent macroscope. The sections were then quantified (3 sections per animal); vessels with tracer accumulation were identified with ImageJ software, and the dsRed fluorescent protein was used to distinguish arteries and veins. The scorer was blind to the experimental condition. We found at 30 minutes post infusion, the CM tracer labeled CSF circulated primarily around arteries (86.2% +/- 4.1% s.d. labeled vessels were arteries, n=560 labeled vessels), but at 120 minutes post infusion the tracer accumulated around more veins (63.1% +/- 7.6% s.d. labeled vessels were arteries, n=850 labeled vessels). This points to an influx of CSF along arteries initially (30-minute group) and subsequent clearance to vein PVSs (120-minute group). Notably, there was still tracer labeling at artery PVSs in the 120-minute group, suggesting some of the tracer is taken up by perivascular macrophages. A subregion analysis was also conducted, by segmenting the brain based on anatomical areas, and counting the vessels labeled with tracer utilizing MATLAB. We found that there was increased vein PVSs labeled in deeper brain areas compared to superficial cortical areas, suggesting that different brain areas may have altered ratios of influx and efflux of CSF, which could further support directional waste clearance. Ultimately, this is one of the first quantitative approaches to demonstrate the existence of artery to vein exchange of fluid and the data shed more light on the organization of glymphatic fluid circulation.

Disclosures: M.J. Giannetto: None. **M. Nedergaard:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.01/B32

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: American Fibromyalgia Syndrome Association
NINDS Grant 1R01NS109529

Title: Fibromyalgia, chronic fatigue syndrome, and multiple sclerosis are associated with low affinity binding of the translocator protein (TSPO)

Authors: *C. L. JONES, J. W. YOUNGER;
Psychology, Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM) are debilitating pain and fatigue disorders with no known etiopathology. They have some symptom overlap with the neuroinflammatory, demyelinating illness multiple sclerosis (MS) that's cause is also unknown, but thought to involve complex gene-environment interactions. Proinflammatory microglial activation in the brain is associated with upregulation of the mitochondrial translocator protein (TSPO) 18 kDA. Positron emission tomography (PET) of TSPO is therefore used to detect neuroinflammation in-vivo. Second generation TSPO ligands are known to demonstrate significant interindividual binding variability due to a single nucleotide polymorphism (snp) rs6971 on the *TSPO* gene that results in a substitution from alanine (Ala) to threonine (Thr) and leads to three genotypes (C/C, C/T, and T/T) (Owen et al. 2012). While collecting data for a TSPO PET study, we observed that patients with ME/CFS, FM, and MS more often presented with the snp (C/T and T/T) than healthy controls. We therefore assessed whether this polymorphism was statistically associated with group membership and severity symptoms. A total of 86 participants were included in the present analyses: 31 FM, 21 ME/CFS, 11 MS, and 24 healthy controls. All participants were female with a mean age of 42.24 (SD = 12.90). Blood was collected into 4mL EDTA-coated tubes. Genotyping was performed with Sanger sequencing. Participants completed questionnaires to assess pain (Brief Pain Inventory), fatigue (DePaul Symptom Questionnaire), anxiety, and depression (Hospital Anxiety and Depression Scale). The relationship between group (ME/CFS, FM, MS, and healthy controls) and rs6971 genotype (C/C (Ala/Ala), C/T (Ala/Thr), or T/T (Thr/Thr)) was analyzed using Fisher's exact test. Whether the rs6971 polymorphism was associated with symptoms was assessed with Mann-Whitney U tests. There were 48 C/C, 30 C/T, and 8 T/T genotypes in the sample. The results of Fisher's exact test indicated a significant association between genotype and group ($p = 0.037$). Participants with ME/CFS, FM, and MS were more likely to exhibit the polymorphism at rs6971 compared to healthy controls. Across all participants, presence of the polymorphism was associated with higher depression scores ($z = 3.03$, $p = 0.003$) and greater fatigue severity ($z = 1.99$, $p = 0.046$). To our knowledge, this is the first study to find a greater frequency of the rs6971 polymorphism in these disorders. Given the purported role of TSPO in steroid synthesis it may represent a target for future treatment trials in these disorders.

Disclosures: C.L. Jones: None. **J.W. Younger:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.02/B33

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: EU Horizon Europe Program under the specific Grant Agreement 101147319, EBRAINS 2.0 project
Swiss National Supercomputing Centre (CSCS)
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Title: Mapping brain lesions to conduction delays: the next step for personalized brain models in Multiple Sclerosis

Authors: *C. MAZZARA[1,2], A. ZIAEEMEHR[3], M. HASHEMI[4], M. ANGIOLELLI[5], V. K. JIRSA[6], P. SORRENTINO[7];
[1]Med., Univ. of Palermo, Palermo, Italy; [2]National Research Council, CNR, Palermo, Palermo, Italy; [3]Inst. For Advanced Studies In Basic Sci. (, Zanjan, Iran, Islamic Republic of; [4]Inst. de Neurosci. des Systèmes- Inserm UMR 1106, Aix-Marseille Univ. Faculté de Médecine de la Timone, Marseille, France; [5]Campus biomedico Roma, Roma, Italy; [6]Inst. De Neurosciences Des Systemes UMR1106, Marseille, France; [7]Aix-Marseille Univ., Marseille, France

Abstract: Multiple sclerosis (MS) is a complex autoimmune disorder affecting the central nervous system (CNS), characterized by a wide range of clinical presentations. Structural damage to the myelin sheath, leading to a decrease in conduction velocities, is a fundamental pathological mechanism in MS. However, the relationship between the extent of myelin lesions and the resulting conduction delays remains unclear, as lesion volume alone is insufficient to predict clinical disability. In this study, we employed large-scale brain models and Bayesian inversion to investigate how myelin lesions contribute to prolonged conduction delays [1]. Each participant underwent MEG and MRI, and detailed white matter tractography analysis was performed. We constructed a lesion matrix indicating the percentage of lesions for each white matter tract in every patient. Utilizing a large-scale brain model, neural activity in each region was modeled using Stuart-Landau oscillators with damped oscillations, coupled according to empirical connectomes [2]. We proposed a mathematical function to describe the relationship between conduction delays and the percentage of structural damage in each white matter tract. By employing deep neural density estimators [3], we inferred the most probable relationship between lesions and conduction delays. MS patients consistently exhibited reduced power within the alpha frequency band compared to healthy controls. The function relating lesions to edge-specific conduction delays, modulated by the parameter alpha, resulted in shifts in the power spectra. We observed a strong correlation between the inferred alpha parameter and the empirically observed alpha peak. Interestingly, the most probable inferred alpha for each subject was inversely proportional to the observed alpha peak, while power peaks themselves did not correlate with total lesion volume. This study provides novel insights into the topography-specific impact of myelin lesions on conduction delays, contributing to the personalized modeling of MS pathology.
References 1. Sorrentino, Pierpaolo, et al. "The virtual multiple sclerosis patient: on the clinical-radiological paradox." *medRxiv* (2023): 2023-12. 2. Cabral, Joana, et al. "Metastable oscillatory modes emerge from synchronization in the brain spacetime connectome." *Communications Physics* 5.1 (2022): 184. 3. Hashemi, Meysam, et al. "Amortized Bayesian inference on generative dynamical network models of epilepsy using deep neural density estimators." *Neural Networks* 163 (2023): 178-194

Disclosures: C. mazzara: None. **A. Ziaeemehr:** None. **M. Hashemi:** None. **M. Angiolelli:** None. **V.K. Jirsa:** None. **P. Sorrentino:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.03/B34

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Discordant EBV-specific immune responses in Multiple Sclerosis patients treated with anti-CD20

Authors: *I. EDMONDSON, R. ALFONSO, S. A. SADIQ, A. DE OLIVEIRA;
Tisch MS Res. Ctr. of New York, New York, NY

Abstract: Multiple sclerosis (MS) is a long-lasting immune-mediated inflammatory disease characterized by the specific targeting of the neuron-protective myelin sheath of the central nervous system (CNS). Infection with Epstein-Barr Virus (EBV), a common gamma-herpesvirus that infects B-cells, has been shown to be necessary but not sufficient for disease development. Moreover, a dysregulated EBV-specific immune response is observed in MS patients compared to healthy individuals including higher anti-EBV antibody levels (especially against the latency protein EBNA-1) and abnormal EBV-specific T-cell response. Although the role of EBV in MS disease remains unclear, misfiring of CNS autoantigens through EBNA1-driven molecular mimicry has been proposed as a possible mechanism of pathogenesis. Current MS therapies prioritize the use of highly efficient disease modifying treatments (DMTs) like B-cell depleting anti-CD20 monoclonal antibodies. Although considered immunomodulatory in nature, the actual mechanisms involved in the beneficial action of these therapies remain largely unknown. In this study, we analyze the humoral and cellular immune responses against EBV in MS patients treated with anti-CD20 compared to healthy controls. This was achieved by measuring anti-EBNA1 immunoglobulin levels using an immunoassay, and the number of cytokine-releasing EBV- and cytomegalovirus (CMV)-specific T-cells by applying a FluoroSpot assay after *ex vivo* stimulation of peripheral blood mononuclear cells (PBMCs) with 15 mer-11 amino acid overlapping peptide pools. Similarly to what has been described in untreated patients, we found that anti-CD20 treated MS individuals had higher levels of EBNA1-specific antibodies compared to healthy controls. In contrast to the humoral response, we found reduced levels of pre-existing T-cell responses against EBV and CMV in anti-CD20 treated MS patients, suggesting a general interference in the memory-associated immune response. These results describe an impact on T-cell functionality during B-cell depleting anti-CD20 treatment without changes in anti-EBNA1 antibody levels. The characterization of EBV-specific immune responses in the context of MS disease and treatment is important to decipher the mechanisms involved in the contribution of EBV to MS disease.

Disclosures: I. Edmondson: None. **R. Alfonso:** None. **S.A. Sadiq:** None. **A. De Oliveira:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.04/B35

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R21 NS121141-01A1

Title: Assessing the Influence of Chronic Cannabis Use on Cognitive-Motor Performance and Brain Structure and Function in People with Multiple Sclerosis

Authors: *Y. LUO[1,2], J. R. DETERS[1,2], C. D. WORKMAN[1,2], P. E. GANDER[1,2,3];
[1]Dept. of Hlth. & Human Physiol., Univ. of Iowa, Iowa City, IA; [2]Dept. of Radiology, Univ. of Iowa Hosp. and Clinics, Iowa City, IA; [3]Dept. of Neurosurg., Iowa Neurosci. Inst., Iowa City, IA

Abstract: Multiple sclerosis (MS) is the primary cause of disability in working-age adults. MS is associated with disrupted cognitive-motor abilities, including executive dysfunction, impaired attention and memory, postural instability, and fatigue. These deficits lead to reduced functional independence and elevated fall risk. Given the limited efficacy of existing disease-modifying treatments in alleviating these medication-refractory symptoms, approximately 70% of people with MS (PwMS) report using cannabis as an alternative treatment. However, the effects of chronic cannabis use on cognitive-motor performance and brain structure and function remain ambiguous. We conducted a cross-sectional observational study to examine the impact of chronic cannabis use on these cognitive-motor and brain imaging outcomes in PwMS. Cognitive-motor performance was evaluated via relevant cognitive and motor tasks, while brain outcomes were determined by MRI and FDG-PET. Specifically, we measured brain structure with relative regional volume (RRV) and resting-state brain glucose metabolism with relative regional metabolism (RRM). Our initial results indicated no significant differences in all cognitive and motor tasks measured in both cannabis users (CUs, N = 14) and non-users (NUs, N = 7). However, Pearson correlations in CUs revealed a strong inverse relationship ($p < 0.01$, $r = -0.81$) between Patient Determined Disability Scale and scores from the Symbol Digit Modality Test (SDMT), with greater disease severity linked to worse information processing speed and working memory. Moreover, a moderate inverse relationship was identified between PDDS and total recall from the California Verbal Learning Test, suggesting worse episodic verbal learning and memory with higher disease severity ($p = 0.05$, $r = -0.54$). MRI revealed no significant differences in RRV between the CUs and NUs. However, FDG-PET highlighted higher RRM in the subcallosal area, posterior temporal lobe, postcentral gyrus, and lower RRM in the cerebellum ($p = 0.05$ for all comparisons) in CUs. Notably, we also found a positive association between cerebellar RRM and SDMT score ($p = 0.02$, $r = 0.67$), pointing to potential cerebellar involvement in cognitive processing. These findings indicate that chronic cannabis use might result in compensatory changes in brain activity, leading to lower cerebellar RRM and compensatory adaptations of other regions to maintain brain function. Our preliminary data reveal differential effects of chronic cannabis use on brain activity and longitudinal studies aimed at delineating the causal relationships and mechanisms underlying these observations are recommended.

Disclosures: Y. Luo: None. **J.R. Deters:** None. **C.D. Workman:** None. **P.E. Gander:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.05/B36

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: The role ofBetaseron mediated neuroprotection in an animal model of multiple sclerosis by regulating mitochondrial and oxidative stress

Authors: *I. MERCHENTHALER[1], T. K. MAKAR[2], J. BRYANT[3];
[1]Epidemiology, Univ. of Maryland, Baltimore, MD; [2]Neurol., Univ. Maryland, Baltimore, Baltimore, MD; [3]Univ. of Maryalnd, baltimore, MD

Abstract: Betaseron brand beta interferon (IFN-β) is one of the standard disease modifying therapies for multiple sclerosis (MS). Early treatment initiation in IFN-β therapy appears to reduce brain atrophy and long- term disability suggesting a neuroprotective effect. While studies suggest an effect on blood brain barrier (BBB) integrity and reduced inflammation in MS, the mechanism for neuroprotection by IFN-β has not been identified. S Apoptosis initiated by mitochondrial oxidative stress may be an important general mechanism in neurodegeneration and studies suggest that mitochondrial stress could play a role in the pathogenesis of MS. IFN-β, an approved treatment for MS, produces however only a partial clinical response due to its short serum half-life and limited ability to cross the BBB. We have developed a means of delivering the IFN-β gene both systemically and into the central nervous system (CNS) using bone marrow stem cells (BMSCs) as a vehicle and examined the therapeutic efficacy of this approach in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. A retroviral expression vector (PLNX-IFN-β) was used to stably transfect virus producer PA317 cells to generate retrovirus containing the IFN-β gene which then was used to transduce BMSCs. IFN-β engineered BMSCs were transplanted (i.v.) into mice that then were immunized with myelin oligodendrocyte glycoprotein (MOG_{35-55} peptide) to initiate EAE. Makar.et.al. J Neuroimmunol,196:67-81 2008.) Our hypothesis is that the neuroprotective effect of IFN-β, in the EAE model of MS, is mediated by a reduction in neuronal mitochondrial dysfunction and axonal loss. Now, we examined the effect of IFN-β on EAE and found reductions in clinical and pathological severity as well as a reduction of markers for inflammation, demyelination, axonal loss, mitochondrial function, oxidative stress and apoptosis in the lumber region of EAE mice after 38 days of EAE induction. Our study revealed that BMSCs-based IFN-β gene delivery into the CNS of EAE mice has a therapeutic effect resulting in a reduction in the frequency and severity of the disease during acute and chronic phases by decreasing inflammation and suppressing demyelination. Our data also demonstrate that IFN-β enhances immunomodulatory and neuroprotective effects in EAE by regulating mitochondrial function, providing tropic support and axonal protection by regeneration of neural elements. The dynamic factors regulated

by IFN-β may constitute a beneficial microenvironment against EAE. This gene delivery approach may have implications in the future for treatment of MS.

Disclosures: I. Merchenthaler: None. **T.K. Makar:** None. **J. bryant:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.06/B37

Topic: C.06. Neuromuscular Diseases

Support: NIH-NINDS (R01 NS065808, R01NS127403)
Legacy of Angels Foundation
European Leukodystrophy Association
Spring 2023, Fall 2023, and Spring 2024 UIC Honors College Undergraduate Research Grants

Title: Local Galactosylceramidase Deficiency in Focal Multiple Sclerosis Brain Lesions

Authors: *J. J. WHITEHAIR, N. SALDIVIA, D. ZELADA, E. R. BONGARZONE; Univ. of Illinois Chicago, Chicago, IL

Abstract: Deficiencies in the lysosomal enzyme galactosylceramidase (GALC) leads to the pathogenesis of Krabbe Disease (KD) through an inability to metabolize psychosine. Psychosine accumulation is cytotoxic and leads to the diffuse death of oligodendrocytes throughout the central nervous system (CNS), demyelinating axons. While our lab has developed a gene therapy protocol that can significantly ameliorate the presentation of KD, long-surviving animal models developed focal demyelinating lesions strongly resembling those seen in multiple sclerosis (MS). These lesions exhibited local deficiencies in GALC as well as heightened psychosine concentration. Notably, it has been found that on average MS patients have a two-fold downregulation in GALC expression compared to controls. Understanding the origin and progression of MS is necessary due to its severe neurological impact, unknown etiology, and lack of any effective treatments. Therefore, our study aims to explore if GALC dysfunction and psychosine accumulation might correlate with the formation of the lesions seen in MS. Post-mortem human brain tissues from individuals with and without MS were utilized. Upon characterization, MS brains and lesions exhibited diminished myelination and heightened astrogliosis compared to controls as expected. GALC activity was notably reduced in MS lesions, yet no accompanying psychosine buildup was observed. Additionally, the expression of acid ceramidase, an enzyme required to construct psychosine, was also lower in MS lesions, suggesting decreased psychosine production. While GALC is clearly dysfunctioning in MS, psychosine accumulation does not correlate with the presentations of MS lesions. There exists a possibility that this impairment of GALC may lead to inadvertent effects on lysosomal function contributing to MS pathology aside from psychosine buildup. Here, we elucidate the relationship

between the roles of lysosomes and MS pathology, which may help in devising new therapeutic interventions which target lysosomal pathways.

Disclosures: J.J. Whitehair: None. **N. Saldivia:** None. **D. Zelada:** None. **E.R. Bongarzone:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.07/B38

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch MS Board of Directors

Title: Multiple Sclerosis CSF Recombinant Antibodies Show Polyreactivity and Binding to Glial Cell Lines

Authors: N. CARULLI, A. RAISINGANI, *J. LIN, Q. YAN, S. A. SADIQ;
Tisch MS Res. Cntr NY, New York, NY

Abstract: Background: Definitive antigenic targets for the antibody response in the cerebrospinal fluid (CSF) of people with multiple sclerosis (PwMS) remain elusive. Finding these targets may lead to the cause of MS and an eventual cure for the disease. **Objective:** Using recombinant IgG_1 antibodies (rAbs) produced from MS CSF, we seek to elucidate the MS antibody response. **Methods:** Single MS CSF B/plasma cells were isolated by fluorescence-activated cell sorting (FACS) using markers for CD19+ and/or CD138+. Each cell's immunoglobulin light and heavy chain genes were sequenced, expressed, and purified as full rAbs. Enzyme linked immunosorbent assays (ELISAs) were performed to assess binding to lipopolysaccharide (LPS), insulin, calf thymus DNA, and cardiolipin. In total, 146 rAbs were used and included 52 PPMS, 48 RRMS, 21 SPMS, and 25 rAbs from other neurological diseases. **Results:** An initial screening using all 146 rAbs against LPS, insulin, and calf thymus DNA yielded 11 MS and 5 non-MS reactive rAbs. Of the MS reactive rAbs, 5 showed reactivity to all three antigens: LPS, insulin, and calf thymus DNA. Two MS rAbs showed reactivity against insulin and calf thymus DNA but not to LPS. In total, 7 of the 11 reactive MS rAbs (63.6%) bound more than 1 antigenic target. Of the 5 non-MS reactive rAbs, only 1 rAb (20%) showed reactivity to more than 1 antigen. Additionally, all of the reactive MS and non-MS rAbs were further assayed for binding to cardiolipin. Only one of the reactive MS rAbs showed binding to cardiolipin, thus increasing the number of MS rAbs binding multiple targets to 8 of 11 (72.7%). **Conclusion:** We tested rAbs produced from CD19+ or CD138+ B/plasma cells from CSF of PwMS and non-MS patients against 4 molecularly distinct antigens; LPS, insulin, calf thymus DNA, and cardiolipin. While reactivity against these 4 antigens was found in only 11 of 121 MS rAbs (9.1%), 8 of these 11 rAbs bound more than 1 antigen, a polyreactive rate of 72.7%. In non-MS rAbs, 5 of 25 show reactivity (20%), while only 1 of 5 non-MS rAb bound

more than 1 antigen, a 20% polyreactive rate. MS rAbs appear to be more polyreactive than diseased controls. However, polyreactivity does not necessarily mean a lack of disease specific antigens. Research is ongoing into identifying any disease relevant antigens associated with these polyreactive MS antibodies.

Disclosures: N. Carulli: None. **A. Raisingani:** None. **J. Lin:** None. **Q. Yan:** None. **S.A. Sadiq:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.08/B39

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Brain Health Research Institute at Kent State University

Title: Facilitating Oligodendrocyte Maturation and Safeguarding Myelin Integrity in Multiple Sclerosis via the TET1-BHMT Axis.

Authors: *M. SHALIH MARAICAR[1], K. KNIES[2], S. STERNBACH[3], E. LESCO[2], R. CLEMENTS[2], J. MCDONOUGH[4];
[1]Dept. of Biol. Sci., [2]Kent State Univ., Kent, OH; [3]Kent State Univ., Kent, OH, ; [4]Biomed. Sci., Kent State Univ., Kent, OH

Abstract: Multiple sclerosis (MS), a demyelinating disease characterized by inflammation, neurodegeneration, and impaired oligodendrocyte progenitor cell (OPC) differentiation, presents an ongoing therapeutic challenge. Dysregulation of methionine metabolism has been implicated in MS, leading to decreased levels of key methyl donors such as S-adenosylmethionine (SAM). Our study sought to elucidate a therapeutic strategy targeting methionine metabolism with betaine, focusing on the betaine-homocysteine S-methyltransferase (BHMT) pathway, a key player in restoring SAM levels and facilitating DNA and histone methylation crucial for OPC survival and differentiation. Employing the EAE mouse model of MS, we administered betaine intraperitoneally at peak disability and employed Coherent Anti Stokes Raman scattering (CARS) microscopy to assess myelin sheath composition around lumbar spinal cord axons unstained. Our results demonstrated a significant improvement in motor ability, validated by substantial lipid content enhancement in the betaine-treated mice via CARS microscopy and clinical scoring. ChIP seq analysis unveiled significant BHMT enrichment at over 2,000 genes, including critical regulators of maturation (Sox10 and Olig2) and metabolic genes (Pdk1). Although BHMT mediated DNMTs activation and DNA methylation are associated with transcriptional repression, Sox10 and Pdk1 genes are activated under betaine administration. Proximity ligation assay confirmed BHMT interactions with Ten Eleven Translocation 1 (TET1), a methyl cytosine dioxygenase in the nucleus of OPCs and oligodendrocytes in both murine and human sclerotic lesions, hinting at a broader influence on transcriptional activation in OPCs

through 5'-hydroxymethylation (5-hmC) by TET1 and BHMT, thereby highlighting its role in OPC maturation and BHMT's potential as an epigenetic intervention target. Spatial ATAC RNA seq analysis of genes targeted by DNA 5-hmC is underway which will elucidate deeper insights into OPC maturation and mediated remyelination after betaine administration. Our study underscores the therapeutic potential of betaine-mediated epigenetic modification via the BHMT pathway, showcasing its impact on motor disability, myelin composition, and the intricate regulation of transcription in OPCs. The nuanced interplay of BHMT with DNMT and TET1 emphasizes the versatility of this pathway in influencing both DNA methylation and 5-hmC and mediated myelin repair. This innovative strategy opens new avenues for targeted interventions in MS warranting further exploration of the specific mechanisms underlying 5-hmC and consequent gene activation.

Disclosures: M. Shalih Maraicar: None. **K. Knies:** None. **E. Lesco:** None. **R. Clements:** None. **J. McDonough:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.09/B40

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch Multiple Sclerosis Research Center of New York (private funds)

Title: Role of antibody-mediated complement activation in primary progressive multiple sclerosis

Authors: S. M. KOVALEV, G. L. CIACCIO, N. CARULLI, A. E. MCDERMOTT, A. RAISINGANI, J. LIN, J. K. WONG, ***S. SADIQ**;
Tisch MS Res. Ctr., New York, NY

Abstract: Primary progressive multiple sclerosis (PPMS) affects 10-15% of MS patients and is characterized by progressive neurological disability from disease onset. We previously reported that pathogenic antibodies in cerebrospinal fluid (CSF) are a distinctive feature of PPMS as only recombinant antibodies (rAbs) derived from PPMS CSF, but not from other MS subtypes, induced motor disability and hallmark MS pathology in a novel mouse model (Wong et al., 2023, Brain). Although positive human IgG immunostaining on spinal cords was observed at a significantly higher incidence in PPMS rAb-injected mice, a variety of staining morphologies were observed, and the exact mechanisms by which PPMS rAbs induce pathology remain unknown. Here, we utilized Fc-engineering to investigate whether specific effector functions mediated by the Fc region play a critical role in PPMS antibody pathogenicity. PPMS CSF was obtained via lumbar puncture and B-cells were isolated by fluorescent activated cell sorting (FACS). PPMS rAbs were generated after PCR sequencing, plasmid expression, and purification. LALA-PG or SAI mutations were introduced into the Fc-region to either silence all

effector functions or specifically disrupt complement activation, respectively. Adult female C57BL/6J mice underwent laminectomies at cervical levels 4 and 5, then 3µL of either: (1) PPMS rAbs, (2) PPMS LALA-PG-rAbs, (3) PPMS SAI-rAbs, or (4) saline was injected into the subarachnoid space. At 1 day post injection (DPI), forelimb motor function was assessed, and mice were perfused for histological analysis. All motor testing and histological analyses were performed blinded. At 1DPI, PPMS rAb-injected mice developed significantly impaired forelimb function compared to mice injected with PPMS LALA-PG-rAbs or PPMS SAI-rAbs. Luxol fast blue staining revealed demyelinated lesions in the cervical spinal cords of PPMS rAb-injected mice. Thus far, we have not observed any demyelinated lesions in mice injected with PPMS LALA-PG-rAbs or PPMS SAI-rAbs. Additionally, human IgG immunostaining appeared to be reduced in mice injected with PPMS LALA-PG-rAbs or SAI-rAbs. Overall, our data show that the pathogenicity of PPMS rAbs is reduced when the Fc region mediating complement activation is silenced, suggesting that complement activation is necessary for PPMS rAb-induced motor disability and pathology. Future studies will continue to narrow down the mechanism by which complement activation contributes to disease pathology in PPMS.

Disclosures: S.M. Kovalev: None. **G.L. Ciaccio:** None. **N. Carulli:** None. **A.E. McDermott:** None. **A. Raisingani:** None. **J. Lin:** None. **J.K. Wong:** None. **S. Sadiq:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.10/B41

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: National MS Society

Title: Comparative single cell/nuclei analysis of glial responses in mouse demyelination models and relevance to Multiple Sclerosis pathology

Authors: *E. ABOELNOUR, K. ADAMS;
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Abstract: Demyelinating diseases, such as Multiple sclerosis (MS), are a set of debilitating conditions in which the myelin sheaths around neuronal axons are lost and contribute to neural degeneration. Currently there are no therapies to promote myelin regeneration, though recent mouse studies support that myelin repair, which is robust in mice, is sufficient to decrease neuronal vulnerability. Several mouse models of demyelination have been used to study the endogenous cellular repair processes, mechanisms to augment repair, and to uncover new druggable targets. Toxicity models to induce the loss of oligodendrocytes (OLs), the cells that contribute myelin, are advantageous because they can predictably target the CNS for reversible myelin loss. However it is not clear if different models stimulate distinct glial responses. Single cell transcriptomics is well suited to compare the cellular responses in these models because of

its high resolution and ability to capture cellular heterogeneity. Using published and unpublished data, we have focused on the toxicity models lysophosphatidylcholine (LPC, also known as lysolecithin) and cuprizone to curate a comprehensive integration of all cell types from single cell or single nucleus transcriptomics from the corpus callosum, the CNS white matter tract that connects the two cerebral hemispheres. We observe an enrichment of distinct disease-associated OL (DAO) states in the LPC and cuprizone models. OLs in remyelinated injuries return to a similar homeostatic state but have transcriptional differences to baseline. Additionally, we observe a unique non-immune glial response in OPCs, the progenitor that gives rise to new OLs, specific to the LPC model. We observe a heterogeneous but robust microglial response, and the continued presence of disease-associated microglia when remyelination is purported to be complete. Additionally, we have performed a cross-species integration between our mouse datasets and white matter lesions from the largest-to-date cohort of MS patient samples. We observe that the astrocytic response is stronger in human tissue, whereas microglia are underrepresented compared to the mice, likely as a result of the end point collection of MS tissues. Importantly, we observe that the transcription phenotype of DAO in mice mirrors transcriptional changes in distinct MS lesion types, but additional phenotypes are not recapitulated in the mouse toxicity models. We will discuss specific gene expression differences between mouse and human MS lesions, and suggest ways in which to leverage the advantages of these models for use in remyelination studies.

Disclosures: E. Aboelnour: None. **K. Adams:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.11/B42

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant 1RF1AG062831
NIH Grant 2RF1AG043640

Title: Age-related dysregulation of c1q and cd47 is associated with myelin damage and microglia reactivity in frontal white matter of aging rhesus monkeys

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Abstract: Normal aging, free from the neuron loss of neurodegenerative diseases like Alzheimer's, is accompanied by chronic, sterile neuroinflammation, which incites innate immune signaling and microglia reactivity that is associated with age-related impairment of learning and memory. Although neurons are not lost in aging human or monkey brains, they

accumulate structural damage evidenced by myelin sheath damage and loss of synapses. This damage results in disrupted conductivity, and ultimately circuit disruption associated with cognitive impairment. The underlying mechanisms of structural damages sustained by neurons and axons is not known, but chronic recruitment of the complement system and microglia of the innate immune system during neuroinflammation are likely candidates. While it is possible that myelin damage and synapse loss occur independently but by the same neuroinflammatory mechanism, another possibility is that synapse loss is secondary to myelin damage. The present study used brain tissue from 36 cognitively tested male and female rhesus monkeys ranging in age from 7-32 years to investigate the classical complement pathway in relation to myelin loss and microglia reactivity in the aging cingulum bundle using immunofluorescence and RNAscope. Our findings showed elevated expression of the classical complement cascade initiator, C1q, in microglia cells. At the same time, myelin basic protein expression decreased while increased C1q protein localized to myelin with age. Further, microglia exhibited diverse morphological and protein expression of C1q and phagocytic marker Gal-3 as they shifted towards an inflammatory and phagocytic phenotype with age. Further, we investigated the neuroimmune regulatory protein, CD47, that mitigates excessive phagocytosis and aids in precision of phagocytosis and found a decrease in CD47 localized to myelin in middle age, when myelin damage begins, as well as a reduction in CD47 RNA in myelin-producing oligodendrocytes with age. Together, these results indicate that at the onset of myelin damage in middle age, there is a reduction in protective CD47 signal on myelin while C1q tagging myelin for elimination increased. Microglia become more reactive with age, evidenced by more cells displaying hypertrophic morphologies along with increased phagocytic Gal-3 signaling possibly related to myelin debris clearance. Overall, these results suggest an age-related dysregulation of innate immune signaling for C1q with a reduction in CD47, which may contribute to a lack of precision in phagocytosis of appropriate myelin debris.

Disclosures: S.A. DeVries: None. **B. Conner:** None. **C. Dimovasili:** None. **M. Medalla:** None. **D.L. Rosene:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.12/B43

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Protease-activated receptor 1 modulates lipid synthesis and homeostasis in the central nervous system

Authors: *W. L. SIMON[1], H. YOON[2], E. TRIPLET[3], L. WURTZ[4], S. C. BUCHL[4], C. CHOI[5], I. A. SCARISBRICK[6];
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Rochester, MN; [5]Mayo Clin., Dept. of PMR, Dept. of Physical Med. and Rehabil., Mayo Clin., Rochester, MN; [6]Physical Med. and Rehabil., Mayo Clin., Rochester, MN

Abstract: Background: Lipids account for approximately half the brain's dry matter and are particularly relevant to myelin, the specialized lipid-rich membrane that facilitates neuronal communication. Myelin degeneration in diseases such as multiple sclerosis has been linked to disrupted lipid homeostasis in the central nervous system (CNS). We have demonstrated that protease-activated receptor 1 (PAR1) knockout mice exhibit accelerated myelin development and increased myelin regeneration in several models of demyelinating disease. We therefore sought to investigate PAR1's role in CNS lipid biosynthesis and homeostasis in health and demyelinating disease. **Methods**: Transcriptional effects of PAR1 presence or absence in healthy mice were investigated by bulk RNA sequencing of spinal cords (SCs) of adult mice and targeted quantitative PCR of SCs at the peak of myelination and early adulthood. GC-MS and LC-MS were used to compare several lipid species in the whole spinal cords and myelin-enriched fractions of PAR1+/+ and PAR1-/- mice at similar timepoints. We then evaluated the impact of PAR1 in the context of disease by inducing demyelination in mice either acutely and focally by lysophosphatidylcholine injection into the white matter of the ventral SC, or chronically by cuprizone feeding for 6 weeks, followed by 4 weeks of recovery and remyelination. Results were assessed by immunohistochemistry. **Results:** Improved myelin production and regeneration in PAR1 knockout mice is linked to increased expression of key regulators of lipid—particularly cholesterol—biosynthesis and homeostasis. PAR1 knockout resulted in increased expression of genes for every enzyme in the mevalonate cholesterol biosynthesis pathway, as well as several genes for lipid processing and transport, including Ldlr, Lcat, and Npc2. GC-MS and LC-MS revealed PAR1-related differences in several lipid species, including total, free, and esterified cholesterol between genotypes. Finally, in our demyelinating disease models, PAR1 knockout differentially regulated expression of transcriptional regulators of lipid metabolism (SREBP1 and SREBP2) and HMGCS1, the rate-limiting enzyme in the cholesterol biosynthesis pathway, in both oligodendrocytes and astrocytes during myelin regeneration.**Conclusions:** These findings indicate that PAR1 is a potential therapeutic target for modulation of cholesterol and other lipids known to be disrupted in several neurodegenerative diseases and support further investigation.

Disclosures: W.L. Simon: None. **H. Yoon:** None. **E. Triplet:** None. **L. Wurtz:** None. **S.C. Buchl:** None. **C. Choi:** None. **I.A. Scarisbrick:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.13/B44

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch Multiple Sclerosis Research Center of New York (private funds)

Title: Establishing a novel CSF-mediated mouse model for MS patients with cerebellar disease

Authors: *G. CIACCIO, A. MCDERMOTT, S. KOVALEV, J. K. WONG, S. A. SADIQ; Tisch MS Res. Ctr. of New York, New York, NY

Abstract: Cerebellar disease (CD) in multiple sclerosis (MS) is indicative of greater disability and a poorer prognosis. MS patients with CD (MS-CD) exhibit a variety of symptoms including tremor and ataxia. Ataxia occurs in approximately 80% of MS patients and is particularly common in those with progressive disease. Our previous *in vivo* studies have demonstrated the feasibility of using patient-derived cerebrospinal fluid (CSF) to create animal models with disease-specific pathology. However, there is currently no model that adequately mimics MS-CD disease pathology. Here, our goal is to establish a CSF-mediated mouse model for MS-CD exhibiting motor impairments and pathological changes like those observed in MS-CD patients. Adult female C57BL/6J mice were trained on the rotarod and baseline measurements were performed at 1 day pre-injection by recording the latency to fall. Mice then received 10µL injections of either: 1) MS-CD CSF, 2) CSF from MS patients without CD, or 3) saline (control) into the cisterna magna. Mice were perfused at 1 day post-injection following rotarod and motor deficit testing. For motor deficit testing, forelimb gripping, reaching, and tail flaccidity were assessed. Cerebella were post-fixed overnight in 4% paraformaldehyde and cryoprotected in 30% sucrose, followed by cryosectioning for histological analyses. All behavioral assessments and histological analyses were performed blinded. In our preliminary studies, MS-CD CSF mice demonstrated a negative trend in rotarod latency and had significantly higher motor deficit scores compared to saline-injected mice. Furthermore, MS-CD CSF induced demyelination as evidenced by cerebellar white matter lesions in the MS-CD CSF-injected mice, which were absent in mice injected with CSF from MS patients without CD. Lastly, MS-CD CSF mice showed microglial activation as indicated by significantly increased Iba1 immunostaining intensities in the cerebellum. This study encourages further investigations into CSF-mediated mouse models for CD in MS. MS-CD CSF triggered coordination and forelimb motor deficits in mice, as well as cerebellar demyelination and microglial activation. Future studies will incorporate additional CSF samples from MS patients with and without CD to validate our model.

Disclosures: G. Ciaccio: None. **A. McDermott:** None. **S. Kovalev:** None. **J.K. Wong:** None. **S.A. Sadiq:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.14/B45

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Cell type dependent role of Nrf2 signaling in regulating neuroinflammation and neurodegeneration in demyelination injury mouse models

Authors: *H. CHEN[1], F. GUO[2];
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Abstract: The transcription factor nuclear factor E2-related factor 2 (Nrf2) is a transcriptional regulator of the anti-oxidative stress response. Intracellular levels of Nrf2 are regulated by proteasome-mediated degradation, a process required by Keap1. The activation of the Nrf2-Keap1 pathway can be considered as a prerequisite for cellular survival under circumstances of increased oxidative stress (OS). Oligodendrocyte loss, OS and subsequent demyelination are hallmarks of multiple sclerosis (MS) lesions and in demyelinating animal models. Literature papers have indicated that global Nrf2 activation ameliorates oligodendrocyte loss, neuroinflammation and axonal damage in an MS mouse model. Nrf2-null mice exhibited increased oligodendrocyte apoptosis and loss, pronounced neuroinflammation and higher levels of axonal damage in cuprizone-induced demyelinating model. There is leukoencephalopathy in aged Nrf2-null mice, with vacuolar degeneration in major brain regions, and compared with widespread astrocyte activation. These studies indicate that Nrf2 plays an important physiological role in maintaining central nervous system myelin and the development of neurodegeneration. Glial cells (oligodendroglia, astroglia, and microglia) play crucial roles in regulating brain homeostasis and neuropath physiology. We hypothesis that Nrf2 deficiency-induced the glial cellular pathology may play important role in neurodegenerative diseases. In the present study, we aim to investigate the role of glial Nrf2-Keap1 pathway system in demyelination and neuroinflammation by using cuprizone demyelinating model. In this study, we will use the Aldh1l1-Cre-ER^{T2}: Nrf2$^{fl/fl}$ and keap1$^{fl/fl}$ mice, Sox10 Cre: Nrf2 $^{fl/fl}$ and Keap1 $^{fl/fl}$ mice, and Temem119-Cre-ER^{T2}: Nrf2 $^{fl/fl}$ and Keap1$^{fl/fl}$ mice to study the effects of Nrf2 loss-of-function and gain-of-function in astrocytes, oligodendrocytes (OLs) and microglia, on brain inflammation and neurodegeneration in cuprizone mouse model.

Disclosures: H. Chen: None. **F. Guo:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.15/B46

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Role of ISGylation in neurons after demyelination.

Authors: *G. MORALES, S. MUHAMMAD, B. CLARKSON;
Neurol., Mayo Clin., Rochester, MN

Abstract: Gloria Morales [1 2], Sara Muhammad [2 3], Benjamin Clarkson [2 3 1]Mayo Clinic Graduate School of Biomedical Sciences, MN, 55905, Rochester, USA.[2]Department of Neurology, Mayo Clinic, Rochester, MN, 55905, USA.[3]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, 55905, USA. **Introduction:** ISG15 is induced in neurons by

demyelination and elevated in MS patient cortical neurons. ISG15 is thought to disrupt ubiquitin signaling through ISGylation. **Hypothesis:** ISGylation contributes to neuron loss in MS by impairing ubiquitin-dependent protein and mitochondrial turnover. **Methods:** ISGylation was induced by IFNg treatment. Protein turnover: cortical neurons were transduced with AAV1.TRE.mCherry-DD to drive Tet-ON expression of the mCherry tagged with a degradation domain (DD). Following induction DD-mCherry is rapidly degraded allowing measurement of proteasome activity. Mitophagy: cortical neurons were transduced with AAV1.Syn.GFP-mCherry-FIS1 (MITO-QC), which targets mitochondria. Upon entry into the lysosome, GFP is rapidly quenched allowing quantification of mitophagy (non-colocalizing mCherry signal). **Results:** In WT but not ISG15 deficient neurons IFNg treatment delayed DD-mCherry degradation. Using the mito-QC reporter, elevated mitochondrial content and mitophagy levels were observed in ISG15 KO cortical neurons. Additionally, prolonged IFNg treatment of neurons decreased levels of non-colocalizing mCherry MITO-QC signal—indicating reduced mitophagy.
Conclusion: IFNg treatment impairs protein and mitochondrial turnover in neurons. Preliminary data suggests these effects are ISG15-dependent.

Disclosures: G. Morales: None. **S. Muhammad:** None. **B. Clarkson:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.16/B47

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Establishment and validation of an in vitro co-culture model to study myelination using human iPSC-derived glutamatergic neurons and oligodendrocytes

Authors: M. BSIBSI[1], A. POPALZIJ[1], M. ZANELLA[1], L. GEERTS[1], M. MUSTERS[1], S. KOSTENSE[1], *M. HERVA MOYANO[2], G. MASTROGIOVANNI[3], I. FERREIRA[3], T. OOSTERVEEN[3,4], D. F. FISCHER[5], M. VLAMING[1];
[1]Charles River Labs., Leiden, Netherlands; [2]Charles River Labs., Saffron Walden, United Kingdom; [3]bit.bio, Cambridge, United Kingdom; [4]Bitbio, Cambrige, United Kingdom; [5]Charles River, Saffron Walden.

Abstract: Oligodendrocytes, the myelinating cells of the central nervous system (CNS), wrap their cell membrane around axons to support rapid nerve impulse conduction. They develop from bipotential Oligodendrocyte progenitor cells (OPCs) which can differentiate *in vitro* into either oligodendrocytes or astrocytes. Oligodendrocyte progenitor cells (OPC) react in human adult CNS to injury by proliferation and migration. Oligodendrocyte dysfunction and disrupted myelin sheaths are involved in the pathogenesis of neurodegenerative disease such as multiple sclerosis (MS) and Alzheimer's disease (AD). Although microglia and astrocytes have been extensively characterized in neurodegeneration, oligodendrocytes have received less attention due to the

complexity of primary oligodendrocyte isolation and culturing. Induced pluripotent stem cells (iPSCs)-derived oligodendrocytes can provide a suitable solution to study differentiation and maturation of oligodendrocytes as well as myelination. Here, we characterized commercially available iPSC-derived oligodendrocytes (ioOligodendrocyte-like cells™) generated by bit.bio using the opti-ox™ technology from human iPSCs. We developed a co-culture *in vitro* model with the iPSC-derived glutamatergic neurons (ioGlutamatergic Neurons™, bit.bio) to evaluate the myelination processes and oligodendrocyte maturation.
Immunofluorescent staining of ioOligodendrocyte-like cells at different time points showed positive staining for key oligodendrocyte lineage markers including Olig2, O4, and SOX2 and myelin markers, including myelin-binding protein (MBP) and myelin proteolipid protein (PLP). At day 3 post seeding the O4+ cells displayed a typical OPC-like morphology. They mature into oligodendrocyte-like cells with characteristic multiple branched processes.
Co-culture of ioGlutamatergic Neurons and ioOligodendrocyte-like cells resulted in increased number of MBP+ cells compared to monocultures of oligodendrocytes in a time-dependent manner. Importantly, MBP+ cells surrounded axons in the co-culture, indicating myelination of neuronal axons.
Taken together, we successfully established a relevant *in vitro* mono- and co-culture myelination model using the iPSC-derived ioOligodendrocyte-like cells and ioGlutamatergic Neurons. These models enable the screening of compounds that modulate oligodendrocyte maturation and myelination, supporting drug development for neurodegenerative and demyelinating diseases, such as multiple sclerosis.

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Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.17/B48

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: EAE model of multiple sclerosis: prophylactic versus treatment fingolimod

Authors: *J. A. ARAUJO[1], A. GANA[2], E. STOJEK[2], D. MOORE-FREDERICK[3], R. WINTERS[2], A. ZOCHOWSKA-KLEPANSKA[4], E. SOKOLOWSKA[5], A. M. BERNARDO[6], J. PRENDERVILLE[7];
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Abstract: Experimental autoimmune encephalomyelitis (EAE) is a robust model of autoimmune inflammatory disease like multiple sclerosis (MS). The EAE model has CNS-related histopathology, motor deficits and inflammatory responses. Fingolimod (Fin), an S1P modulator, is the first oral drug approved for treating MS and is used as a positive control in EAE mice. We aimed to characterize the prophylactic (Pro) and treatment (Tx) effects of Fin in EAE mice by investigating disease progression and assessing neuroinflammatory and axonal damage biomarkers, and histological changes. Female C57BL/6J mice (n=34) were immunized with myelin oligodendrocyte glycoprotein (MOG) in complete Freund's adjuvant followed by pertussis toxin (PT). On Day 2, another PT injection was administered and the Pro group (n=10) received daily administration of Fin. The Tx group started receiving daily Fin when 50% showed clinical symptoms (Day 14). Mice were checked daily for clinical symptoms and body weight (Day 0 -21). Levels of neurofilament light chain (NfL) in plasma and neuroinflammatory biomarkers were analysed by the MesoScale Discovery panel. Inflammatory cell infiltration in the spinal cord was evaluated by H&E staining. Results showed a significant clinical difference between groups ($F(3,36)=6.797$; $p=0.001$). Day 21: Naïve: 0±0, EAE Veh: 2.7±0.5, EAE Pro: 0.25±0.25, EAE Tx:1.4±0.6). The Pro group showed lower daily clinical scoring evaluating the extent of paralysis. 9 out of 10 Pro mice did not develop any clinical symptoms while paralysis progressed in the Tx group. Biomarker results corroborate the clinical scores. NfL plasma levels were increased in EAE Veh animals ($F(3,33)=4.124$;$p=0.01$); Naïve: 1702±764, EAE Veh: 17721±5136, EAE Pro: 3798±907, EAE Tx: 18718±4718. In the brain, increased IL-1β ($F(3, 35) = 3.282$; $p=0.03$) and TNFα ($F(3, 34) = 3.320$; $p=0.03$) were found in EAE Veh compared to Naïve and EAE Pro. (IL-1β: Naïve: 0.34±0.06, EAE Veh: 3.9±1, EAE Pro: 1.3±0.4, EAE Tx: 4.1±1.2; TNFα: Naïve: 0.1±0.005, EAE Veh: 0.9±0.3, EAE Pro: 0.3±0.05, EAE Tx: 1.1±0.3). H&E staining indicated increased penetration of inflammatory cells in the spinal cord in the Tx group compared to the Pro group. A robust preclinical MS model with a consistent positive control is required to advance drug discovery. This study reports that the EAE mouse model can effectively mimic MS symptoms and the temporally-dependent start of a daily dose of Fin can prevent disease onset, development of axonal damage, neuroinflammation and inflammatory cell infiltration in the spinal cord. Therefore, it could be a useful approach to studying treatments that may modify these processes and compare their efficacy with Fin's.

Disclosures: J.A. Araujo: A. Employment/Salary (full or part-time):; Transpharmation Canada Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); InterVivo Solutions Inc. **A. Gana:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Ireland. **E. Stojek:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Ireland. **D. Moore-Frederick:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Ireland. **R. Winters:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Ireland. **A. Zochowska-klepanska:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Poland. **E. Sokolowska:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Poland. **A.M. Bernardo:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Canada. **J. Prenderville:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. Ireland.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.18/B49

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

Support: ALS Association Grant 24-DDC-712

Title: Targeting Chronically Active Microglia: CSF1R Inhibition for Treating Multiple Sclerosis

Authors: M. N. YOUNG, ***Y.-C. LIN**, X. HAN, T. ONG, A. KAPOLIS, Y. CHEN; Myrobalan Therapeut., Medford, MA

Abstract: As the resident immune cells of the central nervous system (CNS), microglia are emerging as key players in the progression of Multiple Sclerosis (MS). Widespread microglial activation is observed in post-mortem patient tissue and animal models of MS. Initially protective, chronically active microglia become detrimental, propagating neuroinflammation and accelerating neurodegeneration. An ideal treatment strategy would preserve neuroprotective microglial function while mitigating abnormal neurotoxicity. The intricate landscape of microglial states poses a challenge for direct manipulation of microglial function through the specific targeting of individual proteins or pathways. An alternative approach involves eliminating chronically active microglia to facilitate repopulation by healthy cells. Leveraging the essential role of CSF1R signaling in microglial proliferation, activation, and survival, multiple groups have sought to repurpose CSF1R inhibitors, originally developed for oncology, to deplete aberrant microglia in neurodegeneration. However, these compounds often suffer from toxicity, off-target effects, and poor brain exposure. We aim to overcome these limitations by (1) developing novel CSF1R inhibitors rationally designed for CNS indications and (2) establishing intermittent treatment regimen whereby chronic, neurotoxic microglia will be periodically depleted allowing for repopulation by new, neuroprotective cells.
We generated small molecule CSF1R inhibitors with best-in-class potency, selectivity, and favorable pharmacokinetic properties, including the ability to efficiently cross the blood-brain barrier. Our lead CSF1R inhibitors demonstrate excellent efficacy in curtailing the proliferation and survival of human iPSC-derived microglia. In a murine model of nerve injury-induced neuroinflammation, our inhibitors effectively dampen microglial activation, as evidenced by a reduction in CD68 immunoreactivity. Significantly, in the C57BL/6J MOG_{35-55} mouse model of experimental autoimmune encephalomyelitis (EAE), our CSF1R inhibitors exhibit notable efficacy under both prophylactic and therapeutic treatment protocols, leading to improvements in disease onset and severity, accompanied by reductions in markers of neuroinflammation and neurodegeneration. Our work provides preclinical support for developing CSF1R inhibitors to suppress chronically active microglia as a therapeutic strategy for MS. Ongoing work includes comparing the efficacy of intermittent treatment with continuous treatment in the EAE model.

Disclosures: M.N. Young: None. **Y. Lin:** None. **X. Han:** None. **T. Ong:** None. **A. Kapolis:** None. **Y. Chen:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.19/B50

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Title: Unraveling Multiple Sclerosis: Insights from Spinal Cord Organoid Models

Authors: *N. DAVIAUD, W. HOLZMAN, T. MEHTA, S. A. SADIQ;
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Abstract: Multiple sclerosis (MS) is an autoimmune neurological disorder characterized by inflammation, demyelination, and neural degeneration affecting both the brain and spinal cord (SC). Although both environmental and genetic factors contribute to the development of MS, the etiology of this disease remains unknown due to the lack of accurate animal models and the relative inaccessibility of human tissue.
While research has focused on the brain, it's important to note that SC damage plays a significant role in MS-related disability. In fact, SC atrophy appears to be more pronounced in progressive forms of the disease and correlates with disability.
Spinal cord organoids (SCOs) have recently emerged as a groundbreaking approach to explore human spinal cord development and related disorders. We have therefore chosen to generate human pluripotent stem cells from both healthy individuals and patients with MS, including primary progressive MS (PPMS), relapsing-remitting MS (RRMS), and secondary progressive MS (SPMS). Our aim is to develop SCOs to examine how the genetic makeup of MS patients influences spinal cord development and the ability of neural precursors to proliferate and differentiate.
We were able to generate SCOs from controls and patients with MS and to assess the behavior of the different neural cell populations. Our preliminary results indicate a dysregulation of the vGlut1+ glutamatergic and GAD67+ GABAergic neuron balance in MS SCO. Similarly, a defect of the GFAP+ astrocyte and Olig2+ oligodendrocyte populations was also detected.
Interestingly, this model allows the studying of ChAT+ motor neurons which are also involved in MS pathology. However, we have not found any difference for this marker in our SCO model of MS. Taken together these results indicate an innate defect of neuronal and glial cells differentiation in MS SCOs.
This study will shed light on the origin and evolution of MS and will help to identify potential targets for therapeutic strategies designed to promote neuroprotection or myelin repair in the different types of MS.

Disclosures: N. Daviaud: None. **W. Holzman:** None. **T. Mehta:** None. **S.A. Sadiq:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.20/B51

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Canadian Institutes of Health Research
MS Canada
University of Alberta Faculty of Medicine and Dentistry

Title: Investigating the role of microglia during cuprizone-induced demyelination

Authors: *K. M. SOUTER[1,2], K. V. LEE[1], A. PANG[1], J. R. PLEMEL[1,3,4,2];
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Abstract: Multiple sclerosis (MS) is a chronic neuroinflammatory condition characterized by demyelination and neurodegeneration. Demyelination occurs after the death of oligodendrocytes, leaving axons vulnerable to damage. Demyelinated lesions are associated with the accumulation and reactivity of microglia. Understanding how microglia cause or regulate demyelination is key to developing therapies that protect against myelin injury. One subpopulation of microglia, interferon-responsive microglia (IRMs), have also been implicated in MS and other neurodegenerative diseases. We hypothesize that microglia are necessary for demyelination. Specifically, damage to oligodendrocytes promotes an IRM response, which exacerbates oligodendrocyte death and demyelination. We used the cuprizone mouse model to investigate microglial-mediated damage to oligodendrocytes and myelin. To determine if microglial ablation reduces oligodendrocyte death and demyelination in the cuprizone model, we depleted microglia via the colony stimulation factor 1 receptor (CSF1R) inhibitor PLX3397 (PLX). Mice consumed cuprizone, PLX, PLX/cuprizone, or control diets. Black-gold II staining of the corpus callosum showed higher levels of myelin in PLX/cuprizone versus cuprizone groups, suggesting microglial involvement in demyelination or delayed myelin clearance. How microglia change throughout demyelination is unknown, but may involve an interferon-responsive microglial state. Understanding the early IRM response may illuminate how microglia promote demyelination. After cuprizone intoxication for two days in Mx1-Cre;Ai9 mice, we detect IRMs in the corpus callosum. IRMs remain in the corpus callosum after one week on cuprizone. This project contributes to the growing recognition of microglial involvement in demyelination and MS. Identifying strategies to modulate the response of microglia may lead to new therapies to protect against demyelination in diseases such as progressive MS.

Disclosures: K.M. Souter: None. **K.V. Lee:** None. **A. Pang:** None. **J.R. Plemel:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.21/B52

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: MWU Start-up funds
MWU One Health Research Stimulus Award

Title: Depletion of microglia worsens symptoms of CNS demyelinating disease and impairs remyelination in the DTA mouse model

Authors: S. LING[1], S. SINGH[1], F. ILYAS[1], S. SAWANT[1], H. ZHANG[2], *M. TRAKA[1,2,3]; [1]Chicago Col. of Osteo. Med., [2]Anat., [3]Col. of Dent. Med., Midwestern Univ., Downers Grove, IL

Abstract: To investigate the demyelination and remyelination processes in the CNS, we previously developed the DTA mouse model that specifically targets the ablation of mature oligodendrocytes by activating the expression of the diphtheria toxin A subunit (DT-A) expression in these cells through tamoxifen injections into young adult *PLP/CreER^T;ROSA26-eGFP-DTA (DTA)* mice (Traka et al., 2010). As a result, the DTA mice develop severe neurological symptoms by 5 weeks post-activation associated with widespread oligodendrocyte death and demyelination in the CNS. Strikingly, these animals fully recover from their motor and physiological defects and display extensive oligodendrocyte replenishment and widespread remyelination of the demyelinated areas by adult oligodendrocyte progenitor cells (OPCs) at approximately 10 weeks post-induction. Given the robust remyelination potential of the young adult DTA mice, it is unclear why remyelination fails in multiple sclerosis. The DTA mouse model has been used here to better understand the role of microglia in the CNS remyelination process. Microglia are the resident macrophages of the CNS that have been shown to be beneficial for remyelination in various myelin mutants by clearing the inhibitory myelin debris and by secreting cytokines that promote the differentiation and maturation of OPCs. Nevertheless, microglia can also play a harmful role in remyelination by promoting inflammation. We previously showed that increased microglia activation occurs in the brains of DTA mice at the peak of the disease (Traka et al., 2010), which correlates with increased expression of neuroinflammatory genes we recently found in the brains of DTA mice by RNAseq. To study the role of microglia in CNS remyelination process, we treated the DTA mice for three continuous weeks starting at 2 weeks post-activation with PLX3397, a small molecule inhibitor of the colony stimulating factor 1 receptor (CSF-1R), that can cross the blood brain barrier and thus rapidly deplete microglia. We discovered that microglia depletion worsens the disease symptoms and leads to increased lethality of DTA mice. Furthermore, PLX3397-treated DTA mice that recovered from disease symptoms showed less efficient CNS remyelination compared to non-treated DTA mice. Overall, our data support the hypothesis that microglia play a positive role in CNS remyelination.

Disclosures: S. Ling: None. **S. Singh:** None. **F. Ilyas:** None. **S. Sawant:** None. **H. Zhang:** None. **M. Traka:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.22/B53

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: FAPESP # 2018/05006-0
CNPq # 303050/2021-7
CAPES # 8887.704147/2022-00

Title: Immunomodulation of Experimental Autoimmune Encephalomyelitis (EAE) with different FGF-2 isoforms and delivery systems

Authors: S. ORTIZ PEÑUELA[1], B. LIMA[1], S. SANTOS[2], A. DUTRA[1], A. OLBERA[3], S. KYRYLENKO[4], R. AMORIM[3], ***A. OLIVEIRA**[1];
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Abstract: Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination, axonal loss and neurodegeneration. The disease is usually characterized by periods of exacerbation interspersed with remissions, so available treatments aim to modify the course of the disease to minimize the risk of relapse. The experimental autoimmune encephalomyelitis (EAE) model is widely used to study immunomodulation in MS, and its use has contributed to new treatment strategies. Fibroblast Growth Factor 2 (FGF-2) is a neurotrophic factor that plays an important role in the development and homeostasis of the CNS, making it an interesting candidate for the treatment of MS. However, one of the major limitations in the use of FGF-2 is its short half-life, which severely limits long-term therapies. However, a computationally engineered FGF-2 protein with improved stability and uncompromised biological function (FGF2-STAB®) has been developed. Alternatively, constant delivery of FGF-2 can be achieved by using a transgenic cell line overexpressing such a neurotrophic factor, and we have a human embryonic stem cell (hESC) line for this purpose. Thus, the present study was designed to evaluate the immunomodulatory and neuroprotective effects of FGF-2 in the C57BL/6J mouse model of EAE by treating MOG35-55 immunized mice intraperitoneally with FGF2-STAB® or intravenously with hESCs overexpressing FGF2 (heavy isoform - 31kDa). The experiments were approved by the Institutional Committee for Ethics in Animal Use (CEUA/IB/UNICAMP/Brazil, protocol number 6026-1/2022). Treatments were administered immediately after disease induction, and weight, clinical scores, and gait analysis (CatWalk System) were monitored until the first remission of disease. Thirty days post induction (dpi), the lumbar spinal cord was harvested for immunohistochemical analysis of glial reactivity and synaptic preservation. Our results showed that animals induced with EAE and treated with both FGF2-STAB® and hESCs showed a significant attenuation of the clinical score already at the 16^{th} dpi (Vehicle 3.00±0.00, FGF2-STAB® 1.88±0.31, FGF-2 hESCs 1.10±0.68, $p<0.05$), improved gait pattern (Regularity Index - 29^{th} dpi, $p<0.0001$), reduced glial reactivity by decreasing the activation of astrocytes and microglia, and promoted the preservation of synaptophysin immunolabeling in the lower motoneuron region (lamina IX of Rexed). Overall, the present data demonstrate the neuroprotective and immunomodulatory potential of FGF-2, either in the thermostable form or in combination with hESC therapy, which may potentially be translated into the clinic to improve the quality of life of MS patients.

Disclosures: S. Ortiz Peñuela: None. **B. Lima:** None. **S. Santos:** None. **A. Dutra:** None. **A. Olbera:** None. **S. Kyrylenko:** None. **R. Amorim:** None. **A. Oliveira:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.23/B54

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

Support: CIHR Project Grant
Canada research chair for Jason Plemel
EndMS Doctoral Studentship

Title: Microglia promote remyelination independent of their role in clearing myelin debris

Authors: *C. BAAKLINI[1], M. HO[1], T. LANGE[1], B. HAMMOND[2], S. PANDA[3], S. ZIA[1], H. K. RANA[3], B. PHILLIPS[6], D. ANTOSZKO[1], J. IBANGA[1], K. LEE[1], M. B. KEOUGH[7], A. V. CAPRARIELLO[8], B. J. KERR[4], J. R. PLEMEL[5];
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Abstract: Multiple sclerosis is an autoimmune disease characterized by demyelination. Several treatments reduce disability in people with MS. Yet, no therapy is available to regenerate lost myelin, a process known as remyelination. Remyelination is linked with decreased disability in people with MS, suggesting the potential for remyelination-enhancing therapies. Remyelination requires an inflammatory response mediated by microglia and monocyte-derived macrophages (MDMs). However, the distinction between how microglia and MDMs regulate remyelination is unclear. We hypothesize that microglia-specific depletion in a gliotoxin model of MS will result in impaired remyelination. We induced focal demyelination by injecting the toxin LPC into the spinal cord of mice. Microglia were depleted by administering diphtheria toxin to mice that expressed a cre-recombinase inducible diphtheria toxin receptor using the CX3CR1CreER mouse line. We obtained tissue at 4, 7, 14, and 21 days post-lesion induction (DPL) and quantified microglia and MDM myelin debris engulfment, OPC proliferation, differentiation and axon remyelination. We found that by 7 DPL, MDMs compensate for microglial loss with respect to myelin debris clearance by expanding in size, density and myelin debris engulfment. By contrast, at 4DPL, OPC recruitment and proliferation was impaired in the absence of microglia. By 14DPL, the absence of microglia was associated with reduced oligodendrocyte accumulation, suggesting that microglia promote OPC differentiation. We also found that early phase microglial depletion, as opposed to late phase depletion, impaired remyelination using electron microscopy. In summary, microglia facilitate distinct stages of remyelination. By

understanding how microglia regulate remyelination, we hope to uncover novel strategies to enhance the microglial response and improve remyelination.

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Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.24/B55

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

Support: CIHR
NSERC
MS Society of Canada
US Department of defense
Faculty of Medicine and Dentistry

Title: Age-impaired remyelination is associated with dysregulated microglial transitions

Authors: *S. ZIA[1], C. BAAKLINI[2], B. HAMMOND[3], N. MEIJNS[7], R. JOHN[1], L. AFUN[1], M. BURR[1], A. RATHOD[1], A. DE FARIA[1], D. ZAVERI[1], S. B. MANESH[9], K. LEE[1], M. HO[1], T. FRIEDMAN[1], A. MAGUIRE[1], O. LA CAPRARA[4], W. TETZLAFF[10], S. SINHA[11], G. DUNCAN[12], A. VORONOVA[1], B. J. KERR[5], M.-E. TREMBLAY[13], J. BIERNASKIE[11], G. SCHENK[8], J. R. PLEMEL[6];
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Abstract: Introduction: Multiple sclerosis (MS) is a neurodegenerative condition that is characterized by multiple demyelinating lesions. Within these lesions, lost myelin may be regenerated through remyelination, where greater remyelination in people with MS correlates with reduced disability. However, remyelination is highly variable, prone to failure, and becomes less efficient with age. Microglia facilitate remyelination while also forming distinct states specific to demyelination and the early stages of remyelination, but it remains unclear how microglia change *throughout* remyelination. ***We hypothesized that distinct microglial states are specific to remyelination and are altered with age.***

Methods: We used the lysolecithin (LPC) mouse model wherein LPC is injected into the spinal cord to induce demyelination followed by robust remyelination. We isolated microglia from LPC-lesioned spinal cords and used single-cell RNA sequencing coupled with advanced bioinformatics techniques to characterize microglial subpopulations. Furthermore, we collaborated with national and international researchers to determine microglial function during remyelination using electron microscopy, transgenic mice and brains from people that had MS. **Results:** We identified distinct regeneration-associated microglial (ReAM) states present during remyelination in young mice, that we named according to their differentially expressed genes. *Igf1* ReAM, *Ccl3* ReAM and interferon responsive microglia (IRM) were present during early remyelination, a time point marked by oligodendrocyte progenitor cell recruitment. Myelin transcript enriched microglia (MTEM) were present during late remyelination may represent a subpopulation of microglia that are pruning newly-laid myelin. We were able to detect MTEM in human MS brain, specifically in the shadow plaque regions—regions with less myelin which could potentially be remyelinating. By middle-age, remyelination declines. We found remyelination in middle-age mice did not result in age-specific microglial states, but rather a delay in appearance of several—but not all—of our defined microglial states. This age-dependent delay in specific microglial states may underlie the age-related decline in remyelination.

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Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.25/B56

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: NMSS Career Transition Award TA-1905-34048
NIH Training Grant 2T32EY013934-21

Title: Comparative assessment of visual pathway degeneration in demyelinating disease

Authors: *G. M. MEY[1,2], J. SHULTZ[1], J. MCGRATH[1], K.-W. CHANG[3], G. XU[1,4], S. WERNEBURG[1,2];
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Abstract: Multiple sclerosis (MS) is an inflammatory demyelinating disease that leads to progressive neuroaxonal loss, circuit degeneration, and neurological decline despite available disease-modifying therapies. Therefore, elucidating underlying mechanisms of neurodegeneration in MS is critical to developing therapeutic strategies to directly promote the protection of neurons and neural circuits. The visual pathway is highly relevant to studying these pathologies as it is one of the most frequently and earliest affected circuits in MS patients. Our lab recently described degenerative pathologies in the lateral geniculate nucleus (LGN) as an important mechanism underlying neural circuit dysregulation, but it is unclear if and how circuit disruption in other regions of the visual pathway affects functional consequences for neural circuits in demyelinating disease. To assess functional changes during demyelinating disease, we performed photoacoustic imaging in mice induced with experimental autoimmune encephalomyelitis (EAE), a model of inflammatory demyelination that is commonly used to study MS. Photoacoustic imaging provides the unique ability to simultaneously assess functional changes in different brain regions of the visual pathway. Our preliminary results indicate an increased latency in multiple visual pathway regions in EAE-induced mice compared to controls. To assess functional changes outside of severe optic nerve and RGC pathology, which occurs in EAE, we also used the cuprizone (CPZ) toxin mouse model of demyelination. To confirm CPZ-mediated pathology in the visual pathway, we assessed myelin proteins and local inflammation in different parts of the pathway relative to the corpus callosum, where CPZ-mediated demyelination is typically studied. Our preliminary results suggest robust pathology but different degrees of demyelination, reactive gliosis, and local inflammation in all compared visual system regions in mice treated with CPZ diet. To assess functional changes across the visual pathway during CPZ-mediated demyelination, photoacoustic imaging will be performed throughout the course of the disease. Together this work will elucidate the extent of degeneration and functional alterations in the visual pathway during demyelinating disease, which will provide impactful information regarding the onset and distribution of neural circuit dysfunction in MS.

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Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.26/Web Only

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: PAPIIT IN210823
APIIT IN206724
CONAHCyT 319880

Title: Altering the onset of myelination in the zebrafish impairs the expression of glial progenitors markers.

Authors: *A. M. OLVERA VIDAL[1], A. CISNEROS-MEJORADO[2], I. LAZCANO[3], A. OROZCO[4];
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Abstract: Altering the onset of myelination in the zebrafish impairs the expression of glial progenitors markers.
Authors:A. M. Olvera Vidal[1*], I. Lazcano [1], A. Cisneros-Mejorado[1], A. Orozco [1, 21]Instituto de Neurobiología, Universidad Nacional Autónoma de México (UNAM), Boulevard Juriquilla 3001, Juriquilla, Querétaro, 76230, México. [2]Escuela Nacional de Estudios Superiores, Unidad Juriquilla, Universidad Nacional Autónoma de México (UNAM), Querétaro, México.
Disclosure:A. M. Olvera Vidal: None, **I. Lazcano**: None, **A. Cisneros-Mejorado**: None, **A. Orozco**: None
Abstract: Central nervous system (CNS) myelination is a process in which the glial cell oligodendrocytes (OL) insulate axons to enhance the speed of neuronal transmission. Neurodegenerative diseases or CNS injuries characterized by neuronal or glial cell loss, present partial and spontaneous re-myelination. During development, myelination is tightly regulated by thyroid hormones (TH) in all vertebrates, but the intrinsic and molecular mechanisms are not entirely understood. Here, we study the disruption of the onset of myelination in the zebrafish (3 days post fertilization) by applying cuprizone (chemical agent that specifically damages OL), with or without the co-administration of T3 (the main TH) or iopanoic acid (TH synthesis inhibitor) in a 5 h acute treatment. To analyze myelin patters, we used Black-Gold II staining and found a depletion of its content at 4 days after the acute cuprizone treatment, with no apparent myelin recovery with T3 or iopanoic acid co-treatments. In consonance, the expression of the myelin structural proteins (*mbpa* and *plp1b*) was depleted. However, an enhanced expression of multi-potent neural stem cell- (*sox2, gfap*) or OL lineage (*olig2*) markers was observed in cuprizone + T3 treated groups. Interestingly, *dio2* and *dio3* the TH-activating/inactivating enzymes, were up- and down-regulated respectively by cuprizone, suggesting a higher TH demand upon myelin damage. These preliminary results suggest that TH driven molecular alterations could be triggered in the glial progenitor pool of damaged OL that could either increase their maturation or myelin synthesis in existing OL. Understanding these mechanisms could provide clues to unveil the knowledge of the endogenous CNS re-myelination, key during neurodegenerative diseases.

Disclosures: A.M. Olvera Vidal: None. **A. Cisneros-Mejorado:** None. **I. Lazcano:** None. **A. Orozco:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.27/B57

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Undergraduate Research Opportunities Program (UROP)

Title: Pre-clinical Model of Pelizaeus-Merzbacher Disease: In Vivo Study in Mice

Authors: *A. TRENDOV[1], A. GOW[2];
[1]Wayne State Univ., Shelby Township, MI; [2]Ctr. Mol. Med. & Genet, Wayne State Univ. Sch. Med., Detroit, MI

Abstract: Alexandar Trendov5/9/2024**Pre-clinical Model of Pelizaeus-Merzbacher Disease: *In Vivo* Study in Mice**Pelizaeus-Merzbacher Disease (PMD) is a rare neurodegenerative disorder affecting the brain's white matter, classified as a leukodystrophy, primarily affecting the myelination process in the central nervous system (CNS). PMD is principally caused by mutations of the *Proteolipid Protein 1 (Plp1)* gene located on the X chromosome—responsible for encoding proteolipid protein 1 (PLP1), the major component of myelin. The most prevalent mutations observed in PMD patients are duplications and triplications of the *Plp1* gene, leading to an overexpression of proteolipid protein causing cellular toxicity and death of oligodendrocytes, inevitably resulting in hypomyelination of the CNS. In attempts to alleviate the disease's symptoms in these transgenic mice, we hypothesize that an intracerebral injection of an adeno-associated virus (AAV) containing an inhibitory short-hairpin RNA sequence (shRNA) into the lateral ventricles of male perinatal mouse pups between the ages of 4-6 days old will suppress overexpression of PLP1 and reduce cytotoxicity. Therefore, this exploratory study aims to regulate PLP1 levels in mutant mice as a potential treatment strategy for PMD patients. The effectiveness of the AAV treatment is evaluated through various behavioral assessments including forearm strength test, rotarod test, and lifespan measures. Because PMD is an X-linked disease, this study uses male mice that are tested from 1 to 6 months of age. The control group consists of 12 wild types (WT), 4 heterozygotes (HT), and 52 homozygotes (HM) mice without the AAV injection. The experimental group contains mice injected with either an active (A) or scrambled (S) shRNA sequence. This group consists of WTa (n=3), HTa (n=12), HMa (n=26), WTs (n=3), HTs (n=6), HMs (n=8). Despite rigorous experimental procedures, the observed outcomes of the experiments fail to exhibit clear distinctions between the control groups and those treated with adeno-associated virus. Moreover, the lifespan of the mutant mice did not show any statistically significant alterations following treatment. These findings underscore the challenges inherent in assessing the efficacy of the therapy in alleviating symptoms of Pelizaeus-Merzbacher disease. The inconclusive nature of the data suggests that further investigations with refined methodologies are necessary to elucidate the true impact of the treatment. Despite these limitations, this preliminary research serves as a critical foundation for future experiments and studies aimed at refining therapeutic strategies for PMD.

Disclosures: A. Trendov: None. **A. Gow:** None.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.28/B58

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: SynaptixBio Ltd.

Title: Antisense therapeutic suppression of Tubulin alpha 4a rescues H-ABC leukodystrophy in mice

Authors: *J. L. HACKER[1,2], S. SASE[3], P. R. NAPIT[3], S. WOIDILL[3], A. TAKANOHASHI[3], A. D'ALESSANDRO[3], Q. PADIATH[4], E. MARSH[3,5], A. VANDERVER[3,5];
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Abstract: Hypomyelination and atrophy of basal ganglia and cerebellum (H-ABC) is a rare leukodystrophy associated with causal variants in tubulin alpha 4A (*TUBB4A*). The recurring variant p.Asp249Asn (D249N), which impacts most affected individuals, presents in infancy with dystonia, speech deficits, progressive gait impairment, and loss of ambulation during the first decade of life. In this study, we generated and characterized a series of mouse models from our previously published CRISPR-Cas9 knock-in D249N mutant Tubb4a mouse and the asymptomatic Tubb4a KO model (*Tubb4a*$^{KO/+}$): wild-type (WT), *Tubb4a*$^{KO/KO}$, *Tubb4a*$^{D249N/+}$, *Tubb4a*$^{D249N/KO}$ and *Tubb4a*$^{D249N/D249N}$ mice in order of increasing phenotypic severity. The *Tubb4a*$^{D249N/D249N}$ mice showed severe progressive motor deficits, myelin, and neuronal deficits with survival up to ~P35-P37. The compound heterozygote *Tubb4a*$^{D249N/KO}$ mouse demonstrated slower progressing motor, myelination, and neuronal deficits with a mean survival of ~P108-P110. Importantly, we confirmed that *Tubb4a*$^{KO/KO}$ mice exhibit no deficits in myelin, neuronal, and motor skills (n=20) with normal survival (Mean survival = P600-720). Overall, disease severity correlates with the expression of mutant Tubb4a and relative preservation of WT tubulin. Thus, suppressing Tubb4a expression might provide a general therapeutic strategy for H-ABC. To evaluate the translational potential of this strategy, we generated and identified *Tubb4a*-targeted antisense oligonucleotides (ASOs; ~100 ASO candidates) that selectively reduced Tubb4a *in vitro* with no toxicity. Potential ASO candidates (~8) were injected in post-natal wildtype mice *in vivo* via an intracerebroventricular (i.c.v) route at 15µg/g dose to assess *Tubb4a* downregulation and both neurological and systemic toxicities. A selected ASO candidate (18-3) demonstrated no neurological or systemic toxicities and showed dose-dependent Tubb4a downregulation at 5, 15, and 20µg/g. Importantly, single i.c.v. administration of ASO 18-3 into postnatal *Tubb4a*$^{D249N/KO}$ mice at a 20µg/g dose drastically extended the lifespan more than 3-fold (Mean survival = P318-P365), reduced seizures and dystonia. Across a range of behavioral tests, *Tubb4a*$^{D249N/KO}$ ASO-treated mice exhibited significant improvement in motor deficits. ASO treatment in *Tubb4a*$^{D249N/KO}$ mice resulted in robust restoration of myelin proteins and oligodendrocytes. Electrophysiological studies demonstrated that this restored myelin is functional, based on improved visually evoked potentials. This is the first preclinical proof-of-concept for Tubb4a suppression via ASO as a disease-modifying therapy for H-ABC.

Disclosures: J.L. Hacker: None. **S. Sase:** None. **P.R. Napit:** None. **S. Woidill:** None. **A. Takanohashi:** None. **A. D'Alessandro:** None. **Q. Padiath:** B. Contracted Research/Research

Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Merck. **E. Marsh:** 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.; Stoke Therapeutics, Zogenix/UCB Pharmaceuticals, Acadia Pharmaceuticals, Marinous Pharmaceuticals, Novartis Pharmacueticals. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIH, Penn Orphan Disease Center, RettSyndrome.org, Reverse Rett, International CDKL5 Research Foundation. Other; Medscape, France Foundation. **A. Vanderver:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Takeda, Shire, Sanofi, Affinia, Ionis, Eli Lilly, Boehringer ingelhiem, Biogen, Sana, SynaptixBio, Orchard, Passage bio, Homology, NINDS, NCATS, PMD Foundation, H-ABC Foundation, AGSAA. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Myrtelle, Homology, Takeda, Eli Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); License for AGS Severity Score, AGS newborn screening and diagnostic biomarkers, ASO therapy in H-ABC.

Poster

PSTR105: Multiple Sclerosis, Leukodystrophies, and Oligodendrocyte Myelination

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.29/B59

Topic: C.06. Neuromuscular Diseases

Support: NSTC-109-2314-B-195-015-MY3

Title: Intracranial delivery of Galc Rescues Demyelination of CNS and PNS and Prolongs Lifespan in Murine Globoid Cell Leukodystrophy

Authors: *D. LIN;
Mackay Mem. Hosp., Taipei, Taiwan

Abstract: Globoid cell leukodystrophy (GLD) is an inherited lysosomal storage diseases caused by mutations in the GALC gene, which encodes lysosomal galactocerebrosidase. Lack of GALC activity results in accumulation of cytotoxic psychosine, aggregation of P62 and ubiquitinated proteins, prominent neuroinflammation, leading to global progressive demyelination of both CNS and PNS and death in early infancy. In present study, adeno-associated virus (AAV) vectors containing Galc were injected intracranially into brain of neonatal twitcher mice, a murine model of GLD, to determine therapeutic efficacy. Twitcher mice treated AAV-Galc contained suprophysiological levels of Galc activity in the brain, spinal cord, and sciatic nerves. In comparison to the controls, remarkable neuroinflammation including astrocytosis and

microgliosis, which was hall mark of pathogenesis in twitcher mice, was prevented in AAV-treated twitcher mice. The accumulation of insoluble p62 and ubiquitin aggregates in white matters of twitcher mice was spared by administration of AAV-Galc in the AAV-treated mice. In line with the rescue of neuroinflammation and autophagy dysfunction by AAV-mediated therapy, myelination of white matters in brain of treated twitcher mice was compatible with that of wild-type mice. Analysis of electron microscopy revealed well myelination in sciatic nerves of AAV-treated twitcher mice, while untreated twitcher mice demonstrated decrease of total myelinated axon relative to the wild-type mice. The longevity of AAV-treated twitcher mice was extended that maximal lifespan was more than 2 years compared with the untreated twitcher mice died around 38-42 days of age.This study demonstrates that monotherapy of AAV-mediated Galc enzyme replacement is sufficient to rescue the hallmark pathologies of GLD and phenotype in the mouse model. These results support clinical translation to address a AAV-mediated gene therapy to rescue demyelinating neurodegeneration and lysosomal storage diseases.

Disclosures: D. Lin: None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.01/B60

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

Title: Evaluation of human induced pluripotent stem cell (hiPSC)-derived tri-culture as in vitro model for Alzheimer’s Disease

Authors: *I. ONOFRE[1,2], C. VAN BERKEL[2], L. SMIT[2], **S. JAIN**[2];
[1]Ncardia, Leiden, Netherlands; [2]Ncardia Services BV, Leiden, Netherlands

Abstract: The development of physiologically relevant models for Alzheimer’s Disease (AD) remains a challenge with an unfilled gap in translatable human-based platforms. Ncardia developed human tri-culture models composed of neurons, astrocytes and microglia derived from iPSCs, resembling physiological conditions that allow modulation of neuroinflammation and neurodegeneration in vitro in the context of AD. In a first step we identified relevant triggers as α-beta (amyloid-beta) and TAU species capable of inducing cellular responses specific to AD pathology in cultures of microglia. Microglia cultures exposed to these triggers released higher levels of pro-inflammatory cytokines, exhibited higher and faster phagocytic activity, assessed by uptake of pHrodo Bioparticles and changed morphology to ameboid shape. In a next step, we established a tauopathy model in the tri-culture system, by inducing the phosphorylation (pTAU), misfolding and aggregation of TAU, using different recombinant mutant TAU (pre-formed fibrils) PFFs. This approach enabled a multi-parametric readout of neuronal and glial phenotypes including activation of microglia and astrocytes in the tri-culture, and release of pTAU and NfL (neurofilament light chain) in the supernatants. In this model we observed

increased levels of phagocyted pTAU by microglia, mostly dependent on the phagocytosis of neurons expressing pTAU and also increased levels of release of IL-6, TNF-α, IL1-β and IL-18. Together, these observations support a neurodegenerative phenotype, typical of tauopathies in which secreted or engulfed pTAU activates microglia initiating the neuroinflammatory cascade. The development and validation of models of relevant biological disease processes, such as microglia-neuron communication, provides insight on cellular interactions. Modeling these cellular interactions play a role in recognizing apoptotic neurons and modulating neuronal activity, which are crucial events in disease progression. Targeting these pathways in human models with a combination of clinically-relevant readouts allows evaluating the ability of therapeutics on rescuing not only primary, but also secondary and tertiary neuro-pathological signatures.

Disclosures: I. Onofre: A. Employment/Salary (full or part-time):; Ncardia Services BV. **C. van Berkel:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **L. Smit:** A. Employment/Salary (full or part-time):; Ncardia Services BV. **S. Jain:** A. Employment/Salary (full or part-time):; Ncardia Services BV.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.02/B61

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

Support: NIH grant R35ns105083
NIH grant R01NS122236

Title: Abnormalities in nuclear pore complex protein, nucleoporin 210, contribute to tauopathy in Alzheimer’s Disease

Authors: *M. DU[1], S. AKERMAN[2], L. RUAN[3], S. O. VIDENSKY[1], C. N. COOK[4], L. PETRUCELLI[5], J. XU[6], J. D. ROTHSTEIN[7];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Neurol., Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins Med. Institutions, Baltimore, MD; [4]Neurosci., Mayo Clin., Jacksonville, FL; [5]Mayo Clin., Jacksonville, FL; [6]Neurol., Dept. of Neurol., Inst. for Cell Engin., Johns Hopkins Sch. of Med., Baltimore, MD; [7]Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Alzheimer’s disease (AD) is the major cause of dementia clinically described as an impairment in memory, thinking, and reasoning, and histologically characterized by the depositions of amyloid beta and microtubule-associated protein tau. Pathological tau has recently been shown to damage the functionality of the nuclear pore complex (NPC) and impair a number of nuclear processes such as nucleocytoplasmic transport. However, given that NPC is composed of multiple copies of over 30 different proteins, known as nucleoporins and plays several roles in maintaining nuclear homeostasis, our current understanding of the molecular mechanisms

underlying this defect and whether/how it affects AD progression is incomplete. Here, we used human induced pluripotent stem cell (iPSC)-derived cortical neurons carrying familial AD mutations (APP-Swedish, PSEN1 L166P) and showed that nucleoporin 210 (NUP210), an integral component of NPC, is reduced on the nuclear envelope and mislocalized into the cytoplasm in a time- and cell type-specific manner. In addition, immunohistological staining of hippocampus from AD patients revealed a profound reduction in nuclear NUP210 expression and along with cytoplasmic mislocalization in both neurofibrillary tangle positive and negative neurons. To investigate the functional consequence of NUP210 loss and its disease relevance *in vivo*, we crossed NUP210 knockout mice with the PS19 animal model of tauopathy. Unexpectedly, NUP210 knockdown in PS19 animals ameliorated their motor impairment, and revealed a trend of increased neuronal density and decreased phosphorylated tau burden in the CA1 region of the hippocampus. Finally, biochemistry assays showed that NUP210 recombinant protein potently facilitated tau aggregation *in vitro*. Taken together, our study suggests that nuclear loss and/or cytoplasmic mislocalization of NUP210 is a pathological event contributing to tauopathy in AD and it provides a novel insight into its therapeutic intervention.

Disclosures: M. Du: None. **S. Akerman:** None. **L. Ruan:** None. **S.O. Videnskiy:** None. **C.N. Cook:** None. **L. Petrucelli:** None. **J. Xu:** None. **J.D. Rothstein:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.03/B62

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

Support: NIH/NINDS: K23NS109284
Roy J Carver Charitable Trust
University of Iowa Graduate College Post-Comprehensive Research Fellowship

Title: Determining the mechanisms of tau degradation in developing neurons

Authors: *M. R. SHIN[1], M. M. WEIS[2], S. L. FIESER[2], N. FIROUZSHAHI[2,3], M. M. HEFTI[2]; [1]Pathology, Univ. Of Iowa, Iowa City, IA; [3]Interdisciplinary Grad. Program in Neurosci. & Pathology, [2]Univ. of Iowa, Iowa City, IA

Abstract: Introduction: While the ubiquitin-proteasome system (UPS) and autophagy are both implicated in Alzheimer’s disease (AD), the relative contributions of these pathways to tau degradation remain unclear. Immature human neurons express high levels of phosphorylated tau similar to that seen in AD but without apparent adverse effects. We therefore sought to identify mechanisms for tau proteostasis in the developing human brain. **Methods:** Human-induced pluripotent stem cell (iPSC)-derived forebrain neurons were cultured following Stem Cell Protocols (equivalent to human second-trimester fetal neurons) and treated with UPS and

autophagy inhibitors. Techniques including RNA sequencing (processed with STAR aligner subreads & DESEQ2), western blotting, and live-cell imaging were utilized to examine changes in tau expression following pharmacological modification of both UPS and autophagic function. For select experiments, we generated and utilized a stable IPSC-derived line expressing eGFP tau. **Results:** We found that inhibition of autophagy had no effect on neuronal native tau. However, proteasome inhibition significantly decreased native tau expression and transcription (unpaired t-test, $p = 0.0094$) & (DESEQ2, $p = <1x10\text{-}4$). We then examined tau expression in our eGFP tau neurons in response to autophagic and proteostatic inhibition. We saw no effect on eGFP tau expression with autophagic inhibition, but we observed a significant accumulation in eGFP tau accumulation in response to proteostatic inhibition (Welch's t-test, time 40 hours: $p = 0.007$). RNA sequencing results indicated that proteasome inhibition led to an upregulation in genes associated with protein refolding and upregulation of 11 protein-modifying genes that have been shown in previous studies to decrease tau expression. **Discussion:** Our study suggests that developing neurons rely on a combination of proteasomal degradation and inhibition of tau transcription to maintain tau proteostasis. The findings of this study are significant because they indicate novel cellular processes specific to tau and waste systems in developing neurons, which adds to our understanding of tau proteostasis, bearing relevance to Alzheimer's disease and related tauopathies.

Disclosures: M.R. Shin: None. **M.M. Weis:** None. **S.L. Fieser:** None. **N. Firouzshahi:** None. **M.M. Hefti:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.04/B64

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

Title: Investigating the electrophysiology effects of tau on hippocampal network activity

Authors: *A. WANG;
Univ. of Warwick, Loughborough, United Kingdom

Abstract: Alzheimer's disease pathology is characterised by the accumulation of misfolded proteins. Tau, a soluble microtubule stabilising protein, which is normally bound to microtubules, detaches and can aggregate to form oligomers and then further to neurofibrillary tangles (NFTs). While the deposition of NFTs correlates well with disease progression, there is growing evidence to suggest that soluble tau oligomers have toxic effects on neuronal properties. In our study, we investigate the effect of tau on the network activity between hippocampal interneurons and pyramidal cells. Following the United Kingdom Animals (Scientific Procedures) Act (1986). Acute Parasagittal hippocampal slices were obtained from P15-21 C57/BL6 mice and transferred into the recording chamber individually. After slices were recovered for at least 1 hour, they were incubated in 133nM sonicated Tau PFFS for 1 hour.

Whole-cell patch-clamp recordings were made from Oriens-lacunosum moleculare (OLM) cells and pyramidal cells (PCs) in the hippocampal CA3 region, identified by their characteristic current-voltage relationship, morphology, and position in the slice. Effects on neuronal properties were recorded.The results indicate differential impacts on network activity between CA3 PCs and OLM cells. While both cell types exhibit depolarisation following tau incubation (OLM control: n = 9, -64.12 ± 1.30 mV, Tau: n = 8, -58.94 ± 2.35 mV; PC control: n = 12, – 64.3 ± 1.59 mV, Tau: n = 9, – 62.8 ± 1.79 mV), only OLM cells showed an increase in rheobase (OLM control: n = 9, 71.7 ± 12.7 pA, Tau: n = 8, 85.4 ± 10.0; PC control: n = 12, 88.2 ± 7.1 pA, Tau: n = 9, 88.2 ± 7.1 pA), suggesting a heightened threshold for action potential generation. This discrepancy could stem from differences in the intrinsic properties or synaptic inputs of CA3 PCs compared to OLM cells. Additionally, the observed increase in mean spontaneous activity amplitude in CA3 PCs (Control: 21.6 ± 1.56 pA, Tau: 40.9 ± 8.26 pA), coupled with a decrease in mean spontaneous activity interval (Control: 501.4 ± 94.0 ms, Tau: 329.1 ± 94.7 ms), suggests a potentiation of excitatory synaptic transmission. In contrast, OLM cells display an increase in mean spontaneous activity interval (Control: 60.2 ± 8.52 ms, Tau: 249.3 ± 86.0 ms), indicating a possible disruption of synaptic activity. (Due to small sample sizes, more data are in the process of being generated before being statistically analysed using Mann-Whitney)Overall, these findings shed light on the complex effects of tau pathology on neuronal excitability and synaptic transmission within the hippocampus.

Disclosures: A. Wang: None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.05/B65

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

Support: JPMJSP2129

Title: Phosphorylation of the proline-rich region regulates tau's microtubule binding and axonal transport

Authors: *R. NAKATA[1], H. MISONOU[2];
[1]Doshisha Univ., Kyotanabe, Japan; [2]Doshisha Univ., Kyoto, Japan

Abstract: Tau is known as a microtubule-associated protein and together with other microtubule-binding proteins, contributes to intracellular trafficking and microtubule polymerization in neuronal cells. In Alzheimer's disease (AD), tau undergoes abnormal hyperphosphorylation and mislocalization, leading to neuronal dysfunction. However, the mechanisms underlying these pathological changes remain elusive. We aimed to elucidate the regulatory mechanisms of tau's microtubule binding and axonal transport, focusing on the role of phosphorylation within the proline-rich region 2 (PRR2) domain, and to understand how these

mechanisms contribute to tau pathology in AD. We employed fluorescence recovery after photobleaching (FRAP) analysis and live-cell imaging using photoconvertible fluorescent protein-tagged tau to investigate tau's microtubule binding and axonal transport in cultured rat hippocampal neurons. Phosphorylation-mimetic and deletion mutants of tau were used to dissect the role of specific domains and phosphorylation sites. FRAP analysis revealed that phosphorylation of the PRR2 domain regulates tau's microtubule binding, with pseudophosphorylated tau exhibiting reduced binding stability. Live-cell imaging demonstrated that the PRR2 domain is critical for tau's axonal transport, and phosphorylation of this domain impairs transport. Interestingly, a tau mutant lacking the microtubule-binding domain (MTBD) still localized to the axon. This finding indicates that tau's localization and transport are not exclusively dependent on microtubule interactions, but likely involve a combination of multiple mechanisms. Inhibition of vesicle transport by Brefeldin A or low temperature disrupted tau's axonal transport, implicating the involvement of the vesicular transport pathway. Our findings demonstrate that phosphorylation of the PRR2 domain modulates tau's microtubule binding and axonal transport. Hyperphosphorylation of this domain, as observed in AD, may lead to reduced microtubule stability and impaired axonal transport, contributing to tau mislocalization and neuronal dysfunction. By uncovering the regulatory mechanisms of tau's microtubule binding and axonal transport, our study provides novel insights into the molecular basis of tau pathology in AD. These findings may guide the development of targeted therapeutic strategies aimed at restoring normal tau function and mitigating neurodegeneration in AD.

Disclosures: R. Nakata: None. **H. Misonou:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.06/B66

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

Title: Recombinant soluble tau aggregates affect the generation of oscillations within the cortico- thalamic network

Authors: *V. A. MITCHELL, M. J. WALL;
Sch. of Life Sciences, Neurosci., Univ. of Warwick, Coventry, United Kingdom

Abstract: The thalamic cortical network (CTC), centred in the thalamus, generates rhythmic oscillations pivotal to normal sleep and brain activity. Dysregulation of these oscillations promotes several pathophysiological states, including absence epilepsy and sleep disorders. Sleep disturbances are a common and highly disruptive symptom of Alzheimer’s Disease (AD), affecting up to 45% of patients. However, the extent of dysregulation of the CTC loop in AD and its impact on sleep abnormalities remain unknown. We aim to explore whether recombinant soluble tau aggregates affect the generation of spindle oscillations in the CTC.
Tau aggregates, a major driver of AD pathology, lead to neuronal dysregulation and cognitive

dysfunction. To model AD pathology, we incubated acute rat (male and female, p.12-24) brain slices with solubilised recombinant tau oligomers. Field recordings were used to record spindle oscillations of the CTC. Oscillations were evoked via stimulation of the internal capsule and were recorded in the ventral basal (VB) thalamus in an interface recording chamber. Tau-incubated slices exhibited greater excitability, as the stimulus strength required to generate oscillations was significantly lower in tau-incubated slices than control slices (n=14). This effect was concentration-dependent with concentrations of tau ranging from 13nM to 444nM. This suggests that tau oligomers can modulate the excitability of the CTC circuitry.
To investigate these effects at a cellular level and to ensure that changes observed were due to modulation of the neuronal circuitry, whole-cell patch clamp recordings were made from thalamocortical neurons in the VB. Tau aggregates shifted the rheobase of cells, de-inactivating T-type calcium channels required for spindle oscillation generation at lower currents compared to control slices. Additionally, we observed increases in firing rate and the number of spindle bursts in tau-incubated slices. Tau aggregates did not significantly alter the resting properties of recorded cells (n=12). Overall, this data suggests that solubilised recombinant tau aggregates modulate the excitability of neurons in the CTC loop, facilitating spindle oscillations at lower thresholds compared to control slices.

Disclosures: V.A. Mitchell: None. **M.J. Wall:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.07/B67

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

Support: NIA R01AG067762
NINDS R01NS082730

Title: The distribution and interaction between tau and protein phosphatase 1 in primary hippocampal neurons

Authors: *M. A. PEREZ, N. M. KANAAN;
Translational Neurosci., Michigan State Univ., Grand Rapids, MI

Abstract: Tau is a microtubule-associated protein involved in microtubule-dependent and independent cellular functions and is distributed throughout many neuronal compartments. Evidence suggests tau acts as a scaffolding protein regulating biological pathways under physiological conditions. Tau plays such a role in regulating protein phosphatase 1 (PP1), a member of the serine/threonine phosphatase family with three isoforms in the mammalian brain (PP1α, β, and γ1). Like tau, PP1 is found in multiple neuronal compartments where it mediates protein dephosphorylation to regulate several biological processes (e.g. axonal transport, synaptic activity, and nuclear function). PP1 functional diversity is driven by its binding to >200

regulatory partners. Physiological and pathogenic tau species are known to interact with PP1 altering its activity and mediated pathways. While data suggest physiological tau acts as a PP1 scaffolding protein that directly modulates PP1 function, several knowledge gaps still exist. Using primary hippocampal neuron cultures from E16 human tau knock-in (hTKI) mice, we established the distribution of tau and PP1 in this model. Confocal microscopy analysis using total tau and PP1 isoform-specific antibodies in DIV 14 hTKI neurons confirmed that tau and PP1 are present within many of the same subcellular compartments. Proximity ligation assays further support a close association between tau and PP1 in neurons with potential isoform-dependent differences. Within the MTBR domain of tau, which is implicated as a key mediator of interaction with PP1α/γ1, are endogenous cysteines at residues 291 and 322. Cysteine-based disulfide bridging contributes to protein conformations and interactions with other proteins. To determine the role of these endogenous cysteines in mediating the tau-PP1 interaction, we generated tau mutants C291A, C322A, and C291A/C322A. WT tau or cysteine mutant tau proteins (C-terminally NanoLuciferase tagged) were co-expressed in HEK 293T cells with N-HaloTag PP1γ1 or a HaloTag only control. Preliminary pulldown and in-cell NanoBRET protein interaction assays suggest removal of the endogenous cysteines reduces tau interaction with PP1γ1 indicating that they may serve a critical mediatory role. Ongoing studies will assess the role of endogenous cysteines in tau on the interaction with PP1α and whether the endogenous tau RVxF-like PP1-binding motifs mediate tau-PP1 interaction. This work will provide additional insight into the complexity of the tau-PP1 interaction and the physiological role of tau in modulating PP1-dependent functions in neurons.

Disclosures: M.A. Perez: None. **N.M. Kanaan:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.08/B68

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

Support: NIH Grant R21AG084065
NIH Grant R25GM075207

Title: Biophysical studies of alzheimer’s disease related proteins in the presence of green tea and turmeric

Authors: *G. ENCARNACION LOPEZ, M. IANNUCCI, M. BUCK;
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Abstract: Alzheimer's Disease (AD) is the leading cause of dementia worldwide and one of the top causes of death in the United States. Around 6 million people in the United States have been diagnosed with this disease, and this number is expected to increase to 13 million in 2050. As the prevalence of this illness continues to grow, there is an urgent need to develop therapies that

focus on modifying the disease-causing mechanisms and preventing its advancement. In this in-vitro study, we explored potential protein targets for AD treatment using natural products EGCG, the active component of green tea, and curcumin, the active compound derived from *Curcuma longa* (turmeric). Specifically, we focused on studying the Tau protein, a member of the microtubule-associated proteins (MAPs) family, which is critical for microtubule stabilization. In particular, it is thought that post-translational modifications such as hyperphosphorylation result in abnormal aggregation of Tau into neurofibrillary tangles, a known hallmark of AD. Cyclin-dependent kinase (Cdk5) and glycogen synthase kinase-3 beta (GSK-3β) are known to aid the aggregation process by hyperphosphorylation of Tau. In addition, possible associations with collapsin response mediator protein 2 (CRMP-2) are thought to contribute to AD progression. To assess interactions between our proteins of interest, we performed MicroScale Thermophoresis (MST) to measure the binding affinity between CRMP-2, Tau, Cdk5, and GSK-3β. Initial MST data indicated binding potential between CRMP-2 and Tau and binding between CRMP-2, Tau, and Ckd5 when they are combined. We also used Phospho-Sens® assay technology to detect the protein kinase activity of Cdk5 (AssayQuant, CSKS-AQT0255K) and GSK-3β (AssayQuant, CSKS-AQT0157). Preliminary kinase assay results show that in the presence of CRMP-2, Cdk5 exhibits a significantly slower phosphorylation reaction ($p < 0.05$), while GSK-3β appeared to have an increased activity. Finally, we performed MST and kinase assays in the presence of curcumin and EGCG, demonstrating that these compounds likely influence the interaction between Tau, CRMP-2, Cdk5, and GSK-3β. In the case of Tau, CRMP-2, and Cdk5, the binding affinity was lower in the presence of EGCG, with a K_D value increase after incorporating EGCG. These results suggest that green tea and curcumin may be potential co-treatments for AD. However, further research is required to better understand the nature of their influences on AD-related proteins and if these are plausible beyond in-vitro settings.

Disclosures: G. Encarnacion Lopez: None. **M. Iannucci:** None. **M. Buck:** None.

Poster

PSTR106: Tau: *In Vitro* Models

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.09/B69

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

Support: NIH/NINDS R01NS128808
NIH/NIA R01AG06943302
NIH/NIA T32AG067952-01

Title: Investigating the effects of tau oligomer exposure and low-level laser therapy on hippocampal neural stem cells

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Abstract: Objective Loss of hippocampal neurogenesis is an early event in the progression of Alzheimer's Disease (AD) resulting in progressive cognitive decline. Preservation of neurogenesis has been shown to correlate with cognitive resilience in a population of non-demented individuals with AD neuropathology (NDAN), and is therefore a potential therapeutic target for the treatment and prevention of AD. One of the early pathological features of AD is the formation and spread of tau oligomers (TauO), aggregates of microtubule-associated protein tau, which have been shown to be biologically active and in some cases toxic, but their direct effects on hippocampal neural stem cells (NSC) are not well understood. Here we investigate the effects of TauO on hippocampal neural stem cells and their differentiation *in vitro* and *in vivo*, and whether a non-invasive nano-pulsed laser therapy (NPLT) can mitigate these effects.**Methods** *In vitro:* Adult rat hippocampal NSCs were exposed to TauO with or without prior treatment with NPLT and seeded on 96-well plates to assess cytotoxicity after 24-hour exposure. To characterize the effects of TauO on NSC differentiation, cells were seeded on laminin-coated chamber slides and fixed at 24-hours and after 7 days of differentiation to characterize their progeny. *In vivo:* 7-10-week-old male and female C57/Bl6J mice were injected ICV with TauO or ACSF, and sacrificed at 24-hours and 7 days post injection. Fixed brain tissue was immunofluorescently labeled for the proliferation marker Sox2 and the immature neuronal marker DCX.**Results** The cytotoxicity assay showed no effect of TauO on LDH release in either NPLT or sham treated NSC. Our differentiation assay showed a substantial increase in cell number caused by TauO exposure and by NPLT treatment in the absence of TauO. Additionally, TauO increased the fraction of NG2+ oligodendrocyte precursor cells and decreased DCX+ neuronal progenitors. In the NPLT treated group, neither control nor TauO treated cells showed any change in NG2+ cell fraction, however both NPLT-treated groups showed decreased DCX+ fraction.In adult mice, ICV TauO injection decreased Sox+ nuclei in the dentate gyrus subgranular zone 24-hours after injection, indicating acute depletion of hippocampal NSC. 7 days after ICV TauO injection, Sox2+ NSC returned to control levels, but DCX+ neuronal progenitors were decreased. **Conclusions** Our results suggest that, although not directly cytotoxic, TauO may play a significant role in the rapid decline of hippocampal neurogenesis seen in AD by aberrantly modulating proliferation and differentiation of NSC, leading to their premature depletion.

Disclosures: K. Johnson: None. **A. Trupp:** None. **A.C. Grant:** None. **R. Esenaliev:** None. **M. Micci:** None.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.10/B70

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

Title: Aggregate formation in p53 and tau proteins

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Abstract: Background Oligomers and fibrils have been well-established as an indicator of Alzheimer's disease (AD). However, there are other protein aggregates besides the well-known tau and amyloid-β that have been potentially shown to be involved in disease development. The protein p53, which is involved in DNA repair, has been shown in previous studies by our lab to form oligomers in AD cases but not in healthy controls. It has also been observed to co-aggregate with tau protein. Owing to the importance of p53 in mitigating damage from diseased cells, loss of function or misfunction of p53 due to aggregation or mislocalisation could contribute to the early stages of AD. Aggregation of p53 and tau in a hetero-oligomer may result in aggregate specific antibodies binding both p53 and tau. This may give mechanistic insights into the proteins' aggregation, while also providing a potential method of inhibiting aggregation *in vivo*. This study examines this common aggregation mechanism. Methods • Using manufactured, recombinant wild-type and mutant p53 and tau proteins, the interaction of p53 and tau was determined based on their immunoreactivity, and compared to amyloid-β. • Conformation cross-reactivity was examined using co-staining of AD mouse model and AD patient samples for both misfolded tau and p53. Results Despite the lack of sequence homology, in-house conformation and aggregation specific p53 and tau antibodies were found to be able to react with both tau and p53 proteins. Mutant p53 was found to react differently to wild-type p53, with reactions varying by mutant. Conclusion The common epitope recognized by p53 and tau antibodies suggests that this is a potential target for antibody therapy. Preventing co-aggregate formation may permit p53 to continue its role, which could, in turn, be a contributing factor in the development of AD.

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Poster

PSTR106: Tau: *In Vitro* Models

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.11/B71

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

Support: MUR PRIN 2022 Grant 2022CFP7RF
Regione Lazio FSE 2014–2020 Grant 19036AP000000019
Regione Lazio FSE 2014–2020 Grant A0112E0073

Title: The eye reveals: tracing neurodevelopment to neurodegeneration in MAPT ivs10+16 mutant iPSC-derived cortical and retinal models

Authors: F. CORDELLA[1], L. MAUTONE[2], S. GHIRGA[3], Y. GIGANTE[3], D. SALERNO[4], E. DEBBI[5], A. SOLOPERTO[6], ***S. DI ANGELANTONIO**[7];
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Abstract: Tauopathies, involving dysregulated tau protein, are crucial in neurodegenerative disorders. Our study explores the impact of the frontotemporal dementia MAPT IVS 10+16 mutation using 2D and 3D human induced pluripotent stem cell (iPSC)-derived cortical and retinal cultures. We aimed to dissect the mutation's effects from neurodevelopment to neurodegeneration phases by employing a novel protocol enhancing neuronal differentiation and maturation.Our results demonstrate that the MAPT IVS 10+16 mutation leads to a significant imbalance in 3R and 4R tau isoforms, favoring 4R expression in mutant organoids. This was corroborated by Real-Time PCR and protein analyses, including immunofluorescence and western blots. Notably, this mutation triggers increased tau phosphorylation, evidenced by enhanced AT8 and pTau181 staining, pivotal in tauopathy progression.Moreover, our analysis revealed a profound impact on neuronal integrity and cytoskeleton stability. Immunostaining for MAP2 and β3-tubulin indicated a fragmented neurite morphology in tau-mutant organoids, suggesting compromised microtubule function and neuronal structure. Further, our gene expression studies through nCounter Nanostring technology indicated significant transcriptional alterations affecting neuronal differentiation and synaptic maturation. Calcium imaging experiments also confirmed impaired network development in tau mutant 2D and 3D cultures.Given the observed downregulation in mitochondrial biogenesis and related stress responses, we explored the therapeutic potential of bezafibrate, a PPAR agonist, in mitigating tau-mutant induced phenotypic defects. Bezafibrate treatment normalized mitochondrial function and enhanced neuronal integrity, evidenced by restored synapsin1 expression and improved neuronal network functionality in tau-mutant organoids. This suggests that targeting metabolic pathways may offer a promising strategy for treating tauopathies.Our study highlights the link between neurodevelopmental defects and neurodegeneration, suggesting that early interventions in tau dysregulation could mitigate later stages of neurodegenerative diseases. Our findings will help the understanding of the pathological role of tau mutations in neurodegenerative diseases and provide a potential therapeutic strategy of interventions targeting tau dysregulation. This research not only advances our knowledge of tauopathy mechanisms but also underscores the utility of human iPSC-derived models in studying complex neurodegenerative diseases.

Disclosures: F. Cordella: None. **L. Mautone:** None. **S. Ghirga:** A. Employment/Salary (full or part-time):; D-Tails srl BC. **Y. Gigante:** A. Employment/Salary (full or part-time):; D-Tails srl BC. **D. Salerno:** None. **E. Debbi:** None. **A. Soloperto:** None. **S. Di angelantonio:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D-Tails srl BC. F. Consulting Fees (e.g., advisory boards); D-Tails srl BC.

Poster

PSTR106: Tau: *In Vitro* Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.12/B72

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

Support: JST Keio-SPRING
The Keio University Doctorate Student Grant-in-Aid Program from Ushioda Memorial Fund

Title: High content screening for modifiers of endogenous wild-type/mutant Tau

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Abstract: Tau protein aggregation is a pathological hallmark in various neurodegenerative disorders collectively known as tauopathies, including Alzheimer's Disease (AD) and frontotemporal dementia spectrum diseases (FTLD-s). Tau gene mutations induce familial diseases, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), characterized by tau aggregation. This study aims to identify modifiers of human WT and/or mutant Tau. This has the potential to identify disease-modifying drugs across tauopathies. To identify human Tau modifiers at multiple levels, such as transcription, translation, protein degradation, and subcellular localization, we developed a high-content screening (HCS) platform targeting endogenous tau using human induced pluripotent stem cell (hiPSC)-derived neurons and screened existing drug compound libraries. First, we fused TagGFP2 to the N-terminus of Tau to monitor the dynamism of endogenous wild-type (WT) tau in hiPSC-derived neurons. In addition, we knocked out endogenous tau or introduced the hTau A152T mutation which increases the risk of both AD and FTLD-s. Next, we differentiated the iPSCs into neurons by overexpressing neuron-enriched miRNAs and a transcription factor, Neurogenin 2. The A152T mutation increased neuronal activity, as measured by Ca2+ imaging, reminiscent of the epileptic phenotype in the hTau-A152T transgenic mouse model. Subsequently, we established an HCS assay in which Z', an indicator of screening platform robustness, was high enough to perform a screening (Z'>0.3). We screened 1165 small compounds by exposing them to hiPSC-derived neurons for 10 days. The readout for initial screening was the TagGFP2 fluorescence intensity quantified by an automated confocal microscope. The initial screening identified 51 compounds capable of suppressing Tau protein expression levels. While some compounds were equally effective in reducing WT and A152T Tau, others were preferentially effective on WT or A152T neurons. Among the identified compounds, three drugs known for common medicinal effects on non-brain organs, share the same target molecule. We discovered that these compounds suppressed total Tau expression, phosphorylated Tau, and human Tau mRNA levels. In conclusion, we have developed an HCS platform for Tau modifiers and identified 51 candidates out of 1165 compounds from the initial screening. We discovered three compounds originally developed for non-neural disease, suppress total Tau, phosphorylated Tau, and human Tau mRNA levels. Though the specific targets of these drugs are under investigation, these can be candidates for Tau-modifying drugs.

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Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.01/B73

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

Title: A Novel Disease-Modifying Immunotherapy for the Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) remains a neurodegenerative disorder that currently has no significant disease-modifying treatment. As the most common form of dementia defined by progressive memory loss, cognitive impairment, behavioral changes, and functional ability alterations, AD inevitably hinders the quality of life of patients and their caregivers. Although AD is a prevalent disease that has been studied for decades, there still is an unmet clinical need for therapeutics capable of reversing and modifying disease progression, serving a purpose beyond symptom management, and a gap in knowledge regarding the body's immune response to the disease. Thus, our goal is to attain a better understanding of the body's immune system in AD as well as broaden the scope of therapeutics available to patients. We seek to present a novel immunotherapy capable of harnessing the body's immune system whilst clearing the brain of the pathogenic peptide, Aβ, and further expand the current knowledge of the body's immune response in AD. Here we developed a new immunotherapeutic bispecific antibody, in the form of a Fc-engineered immunoglobulin G (IgG)-single-chain variable fragment (scFv) conjugate, that binds to human programmed death-ligand 1 (hPD-L1) and Aβ, for modifying the disease status of AD patients. We demonstrated that treatment with our bispecific antibody efficiently targeted multiple factors of disease drivers by modulating the immune system in the brain, improving the clearance of Aβ, and permitting overall cognitive improvement of the humanized PD-L1 and 5xFAD (hPD-L1/5XFAD) mouse. Altogether, our study provided a novel immunotherapy capable of safely modulating disease and valuable insight into the role of the body's immune response in AD. With a deeper understanding of the immune processes in AD, the study will enable our long-term goals of prompting further development of innovative therapeutics and extending the healthy, active years of older adults.

Disclosures: A. Kim: None. **S. Lim:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.02/B74

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

Support: Jeanne B. Kempner Scholarship (2022-2023, C.N.)
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Mitchell Center for Neurodegenerative Diseases
NIA R21 - AG059223 (B.K.)

Title: Functional assessment of Phospholipase D1 using wild-type, transgenic Alzheimer's Disease mice, and human spheroid models: A spatial and temporal mechanism for the progression of neurodegeneration

Authors: *S. SREENIVASA MURTHY[1], C. NATARAJAN[2], K. GARZA[1], S. BUDHWANI[1], S. BOSWORTH[1], J. CURRIE[3], S. MOHANTY[1], M. MALLIPUDI[1], K. SHETH[1], E. WONG[1], P. SHAH[1], T. A. GREEN[5], M. VILLARREAL[1], A. LIMON[6], E. LEE[7], J. ZHANG[7], M. FERRER[7], B. KRISHNAN[4];
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Abstract: Introduction: Phospholipase D (PLD), primarily functions as a lipolytic enzyme breaking down membrane phospholipids. We recently reported an anomalistic increase in phospholipase D isoform 1 (PLD1) in AD postmortem brain samples, compared to control subjects. Moreover, the effect of elevated PLD1 driven by amyloid-β and tau deposits has been well-established in wild type and in 6-month-old 3xTg-AD model mice. In the present study, we assess the novel role of PLD1 in modulating cellular mechanisms involved in synaptic dysfunction in AD. **Methods:** We studied the spatial and temporal expression of PLD1 in 3xTg-AD model mice, treated with a small molecule PLD1 inhibitor (VU0155069), in an age-dependent manner. Furthermore, the brain-region specific mechanisms of PLD1 were evaluated by utilizing adeno-associated viral 2 (AAV2) vectors via intracerebroventricular route in 18- and 24-month-old wild-type and 3xTg-AD model mice. Following VU0155069/AAV2 administration, the mice cohorts were subjected to behavioral studies specific to learning and memory, such as Y-maze, novel object recognition (NOR), and elevated plus maze. Synaptic dysfunctions were studied using high frequency stimulation long-term potentiation (HFS-LTP), by conventional electrophysiology and multi-electrode array (MEA). Finally, the synaptic strength in frozen synaptosomal (P2) fractions was determined by previously standardized novel

in vitro assay called the Fluorescence-Assisted Single Synaptosome-Long Term Potentiation (FASS-LTP). Morphological changes in the synapse were assessed using ImageJ and IMARIS following Golgi-Cox staining, a gold standard for measuring dendritic spine integrity. To deduce the underlying mechanisms, we used brain spheroids developed from human tissue to test the effects of PLD1 inhibition. **Result:** By using pharmacological and genetic approaches we noted differential effects of PLD1 over-expression and attenuation in both WT and 3xTg-AD aged mice models. **Conclusion:** PLD1 contributes to progressive functional deficits associated with synaptic dysfunction by impinging on critical cellular signaling events compromised in early and late stages of Alzheimer's disease.

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Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.03/B75

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

Support: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
Conselho Nacional de Desenvolvimento Científico e Tecnológico
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Serrapilheira Institute (R-2012-37967)

Title: The ketamine metabolite (2R,6R)-hydroxynorketamine rescues hippocampal mRNA translation, synaptic plasticity and memory in mouse models of Alzheimer's disease

Authors: *D. COZACHENCO[1], F. C. RIBEIRO[2], E. K. ARGYROUSI[4], A. STANISZEWSKI[5], S. WIEBE[6], A. AL-CHAMI[7], S. BERMUDEZ[6], E. R. ARSENAULT[7], M. COSSENZA[9], J.-C. LACAILLE[10], K. NADER[6], H. SUN[8], F. DE FELICE[11], M. V. LOURENCO[3], O. ARANCIO[12], N. SONENBERG[6], S. T. FERREIRA[1];
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[9]Federal Fluminense Univ., Niterói, Brazil; [10]Univ. De Montreal, Montreal, QC, Canada; [11]Queen's Univ., Kingston, ON, Canada; [12]Taub Inst., Columbia Univ., New York, NY

Abstract: INTRODUCTION: Impaired brain protein synthesis, synaptic plasticity and memory are major hallmarks of Alzheimer's disease (AD). The ketamine metabolite (*2R,6R*)-hydroxynorketamine (HNK) has been shown to modulate protein synthesis, but its effects on memory in AD models remain elusive. **METHODS:** We investigated the effects of HNK on hippocampal protein synthesis, long-term potentiation (LTP) and memory in AD mouse models. **RESULTS:** HNK activated extracellular signal-regulated kinase 1/2 (ERK1/2), mechanistic target of rapamycin (mTOR), and p70S6 kinase 1 (S6K1)/ribosomal protein S6 signaling pathways. Treatment with HNK rescued hippocampal LTP and memory deficits in amyloid-β oligomers (AβO)-infused mice in an ERK1/2-dependent and, partially, mTORC1-dependent manner. Treatment with HNK further corrected aberrant transcription, LTP and memory in aged APP/PS1 mice. **DISCUSSION:** Our findings demonstrate that HNK induces signaling and transcriptional responses that correct synaptic and memory deficits in AD mice. These results raise the prospect that HNK could serve as a therapeutic approach in AD.

Disclosures: D. Cozachenco: None. **F.C. Ribeiro:** None. **E.K. Argyrousi:** None. **A. Staniszewski:** None. **S. Wiebe:** None. **A. Al-Chami:** None. **S. Bermudez:** None. **E.R. Arsenault:** None. **M. Cossenza:** None. **J. Lacaille:** None. **K. Nader:** None. **H. Sun:** None. **F. De Felice:** None. **M.V. Lourenco:** None. **O. Arancio:** None. **N. Sonenberg:** None. **S.T. Ferreira:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.04/B76

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

Title: Accumulation of Alzheimer's disease specific pathologies in drug resistant epileptic mouse and its impact on cognitive functions

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Abstract: Dementia and epilepsy are in top four primary brain diseases. Progression of both disease processes are entirely different but recent epidemiologic studies have highlighted that there's a bidirectional association between the most common dementia i.e., Alzheimer's disease and late onset epilepsy. Cognitive comorbidities are highly prevalent in epilepsy and often seen as secondary to epilepsy and drug-resistant epilepsy. It is largely unknown that how recurrent seizures favour cognition impairment and progression of dementia in epileptic patients. Similarly, growing clinical evidences indicate that most Alzheimer's patients have subclinical

seizures or aberrant epileptiform. The aim of present study was to explore presence of Alzheimer's disease specific pathologies in drug-resistant epilepsy along with its impact on cognitive functions. Drug-resistant epilepsy was induced by rotenone-corneal kindling method i.e., mice were treated with 2.5mg/kg rotenone along with mild electric shock15mA, 20V, 6-Hz on a daily basis for 15 days. Epileptic mice were treated with standard antiseizure drugs to validate drug-resistance. Cognition was assessed by radial arm maze and passive avoidance tasks. Congo red and silver staining was performed to identify Alzheimer's disease specific pathologies. Acetylcholinesterase assay was performed by the ELISA. Neurotransmitters were analysed by HPLC-ECD. Rotenone-corneal kindled mice showed significant ($P< 0.05$) resistance to standard drugs including lamotrigine, levetiracetam, carbamazepine, phenytoin and valproic acid. Cognitive functions of rotenone-corneal kindled mice was significantly impaired as compared to drug responsive corneal kindled mice. Acetylcholinesterase activity was significantly reduced. Neurochemical analysis showed significant alteration in rotenone-corneal groups as compared to drug responsive corneal kindling group. Histological studies of the deposition of amyloid and tau proteins significantly observed using congo red and silver stain. Accumulation of Alzheimer's disease specific pathologies may contribute to cognition deficit in the drug resistant epilepsy.

Disclosures: A. Kaur: None. **R.K. Goel:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.05/B77

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

Support: NIH Grant R01AG075820
NIH Grant R01AG071587
NSF CAREER 1944053

Title: Systemic effects of ERK signaling pathways inhibitor, PD-0325901, in a mouse model of Alzheimer pathology

Authors: *C. ESPINOSA-GARCIA[1], **D. KOUR**[1], H. XIAO[2], A. TFAILY[1], C. BOWEN[2], R. NELSON[1], U. SRIVASTAVA[1], P. KUMAR[1], S. MALEPATI[1], B. R. TOBIN[4], S. BITARAFAN[4], Y. LI[3], A. F. CHAUDHARY[3], W. ZHANG[3], Z. SONG[3], J. CHEN[3], S. LIANG[3], L. WOOD[4], S. RANGARAJU[1];
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Abstract: Alzheimer's Disease (AD) affects more than 55 million people worldwide and currently has no cure. Large-scale proteomic studies of human post-mortem brains from control, asymptomatic AD and AD-dementia cases nominate the extracellular signal-regulated kinase

(ERK) pathway as a central disease mechanism and a potential target in AD. Recently, our group has demonstrated that ERK is hyperactivated, particularly in microglia but not whole brain tissues in mouse models of AD pathology, and *in-vitro* and *in-vivo* ERK inhibition decreases pro-inflammatory immune responses. This study aims to determine the effects of chronic systemic ERK suppression on pathological hallmarks and microglia transcriptomic signatures in the 5xFAD model of AD. We used 3- and 6-month-old male and female wild-type (WT) and 5xFAD mice, to understand age- and sex-dependent changes occurring in the early and the late stages of the disease. To inhibit ERK, we administered a low-dose of PD-0325901, a highly potent brain-permeant small molecule, in compounded chow [10 ppm] for 3 months. We evaluated cognitive and behavioral changes through the Open field, Morris water maze, and Fear conditioning test. We conducted *in-vivo* PET imaging studies to assess synaptic density using the novel SV2A tracer ^{18}F-SDM-8. Mice were deeply anesthetized, and blood was collected via cardiac puncture to measure neurodegeneration biomarkers (Aβ and Neurofilament light) in plasma. Next, mice were perfused with PBS, brains were removed, longitudinally bisected, one hemisphere was used for molecular and immunohistochemical analysis, while the other was used for microglial isolation, using Percoll density centrifugation, followed by enrichment of CD11b+ magnetic activated cell sorting (MACS), and microglial gene expression will be analyzed by mRNAseq. Our preliminary results show that treatment with PD inhibitor beginning at 3 months of age significantly inhibited ERK activation in 5xFAD female mice and preserved/restored synaptophysin levels, with no effects on Aβ load. Our ongoing analysis will investigate PD inhibitor efficacy to (1) abate microglial/astrocytic activation and neuroinflammatory mediators, (2) prevent synaptic marker loss, (3) modulate pro-inflammatory microglia transcriptomes, and (4) ameliorate cognitive impairments. The insights gained from this research will guide pharmacological studies to achieve ERK inhibition for disease-modification in AD, and impact future cell type-specific mechanistic studies.

Disclosures: C. Espinosa-Garcia: None. **D. Kour:** None. **H. Xiao:** None. **A. Tfaily:** None. **C. Bowen:** None. **R. Nelson:** None. **U. Srivastava:** None. **P. Kumar:** None. **S. Malepati:** None. **B.R. Tobin:** None. **S. Bitarafan:** None. **Y. Li:** None. **A.F. Chaudhary:** None. **W. Zhang:** None. **Z. Song:** None. **J. Chen:** None. **S. Liang:** None. **L. Wood:** None. **S. Rangaraju:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.06/B78

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

Support: CIHR #PJT-162144

Title: Investigating the effects of 17-beta estradiol on NF-κB mediated inflammation and mitochondrial function in Alzheimer's disease

Authors: *P. MISHRA[1,2], E. ESFAHANI[3], P. FERNYHOUGH[1,2], B. C. ALBENSI[4,2,5]; [1]Univ. of Manitoba, Winnipeg, MB, Canada; [2]St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada; [3]St. Boniface Hosp. Albrechtsen Res. Ctr., Winnipeg, MB, Canada; [4]Nova Southeastern Univ., Ft Lauderdale, FL; [5]University of Manitoba, Winnipeg, MB, Canada

Abstract: Introduction: Alzheimer's disease (AD), a neurodegenerative disorder linked to aging, manifests as a complex interplay of factors including inflammation and mitochondrial dysfunction. Amyloid beta (Aβ), a hallmark of AD exacerbates inflammation and mitochondrial dysfunction by activating pro-inflammatory NF-κB signaling, leading to chronic inflammation and metabolic defects, contributing to neurodegeneration. Moreover, the risk of developing AD significantly increases with loss of estradiol (E2), which is associated with the aging process. E2 has been shown to impart neuroprotection in both cell lines and primary cells. Our preliminary studies conducted with primary cortical neurons have found that E2 can improve mitochondrial activity, regulate pro-inflammatory NF-κB activation, as well as protect cells from Aβ mediated neurotoxicity. The *objective* of our study is to investigate the neuroprotective effects of E2 against Aβ-mediated neuroinflammation and mitochondrial dysfunction. **Methods:** Primary cortical neurons from C57BL/6 mouse embryos were isolated and cultured under defined conditions. Glial inhibitor AraC (2μM) was used obtain pure neuronal cultures. AD-like pathology was induced by adding 1μM Aβ, and cells were treated with 10nM E2. We used western blotting to measure the expression levels of proteins: phosphorylated AMPK (pAMPK), PGC-1α and NF-κB IKβα. Cell viability was measured using the MTT assay (abcam #ab211091) according to the manufacturer's protocol. Oxygen Consumption Rate (OCR), an established measure of mitochondrial function was evaluated in live cells using the SeahorseXF24 bioanalyzer. **Results:** Immunocytochemical analysis confirmed that our primary neuronal cultures were >90% pure. E2 treatment increased both; the levels of cellular energy sensor pAMPK and the master regulator of mitochondrial biogenesis PGC-1α. Additionally, E2 elevated mitochondrial function by increasing maximal respiration and spare respiratory capacity in these cells. We also observed a decrease in pro-inflammatory NF-κB activation as E2 decreased the phosphorylation and degradation of NF-κB inhibitory protein IKbα. MTT assay to measure cell viability, revealed that E2 attenuates Aβ-induced neurotoxicity. **Conclusion:** Our findings underline the importance of E2 in modulating mitochondrial function and NF-κB mediated inflammation, and also shed light on its neuroprotective properties against Aβ. The anticipated outcomes of this study hold promise for advancing our understanding of therapeutic strategies in alleviating neurodegenerative diseases, including AD.

Disclosures: P. Mishra: None. **E. Esfahani:** None. **P. Fernyhough:** None. **B.C. Albensi:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.07/B79

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

Support: NICHD Intramural grant

Title: Neurotrophic factor α1/carboxypeptidase E prevents and reverses Alzheimer's Disease pathology in mouse models

Authors: L. XIAO[1], F. FAN[2], X. YANG[1], Y. CHENG[2], *Y. LOH[1];
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Abstract: Alzheimer's Disease (AD) is the most prevalent neurodegenerative disease among the aging population globally. Currently, there is no cure for the disease. Neurotrophic Factor-α1/Carboxypeptidase E (NF-α1/CPE) is increasingly recognized as a pivotal neuroprotective protein that can rescue cognitive decline associated with Alzheimer's disease (AD). Our previous studies reported that delivery of mouse AAV-NF-α1/CPE to the hippocampus downregulated amyloid aggregation, tau pathology, and neurodegeneration, as well as prevented cognitive deficits, in pre-symptomatic 3xTg-AD mice. Mechanistically, NF-α1/CPE increased expression of Bcl2, a pro-survival protein and reduced expression of pro-inflammatory protein Card14 and anti-mitophagy protein Plin4, to mitigate AD pathology. Here we investigated whether a non-enzymatic form of NF-α1/CPE or human NF-α1/CPE have similar effects. Following AAV delivery of non-enzymatic NF-α1/CPE-E342Q and human NF-α1/CPE, AD pathology such as amyloid accumulation and neurodegeneration were prevented in pre-symptomatic 3xTg-AD mice indicating that it functions independent of enzymatic activity. In addition, NF-α1/CPE overexpression rescued the decreased autophagic function and synaptogenesis in 3xTg-AD mice. We then determined if hippocampal delivery of AAV-CPE in post-symptomatic 5xFAD mouse model could reverse AD pathology. Our findings revealed that the AAV-CPE treated 5xFAD mice reversed the increased amyloid plaques, activated microglia, decreased synaptogenesis and impaired cognition, in a dose-dependent manner. We also showed that down-regulation of neuronal NF-α1/CPE expression in 5xFAD mice using the Cre-lox system was highly associated with increased amyloid aggregation, microglia activation, decreased synaptogenesis and impaired cognition. These results indicate that NF-α1/CPE is a key player in controlling AD pathology and illuminated the therapeutic potential of NF-α1/CPE in treatment of AD.

Disclosures: L. Xiao: None. **F. Fan:** None. **X. yang:** None. **Y. Cheng:** None. **Y. Loh:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.08/B80

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

Support: Fonds de Recherche du Québec en Santé
Alzheimer Society Canada
Canadian Institutes of Health Research

Title: Pharmacological stimulation of brown adipose tissue activity protects against cold-induced rise in phosphorylated tau in the 3xTg-AD mouse model.

Authors: *J. VALENTIN[1], M. TOURNISSAC[2], E. PLANEL[3], S. S. HEBERT[4], C. TREMBLAY[5], F. CALON[6];
[1]Neurosci., Ctr. de Recherche du Ctr. Hospitalier Universitaire-Université Laval, Québec, QC, Canada; [2]U968, INSERM, Paris, France; [3]Univ. Laval, Quebec, QC, Canada; [4]CHUL, Neurosci., P0-9800, Laval Univ., Quebec, QC, Canada; [5]Neurosciences, CHUL Researsh Ctr., Quebec, QC, Canada; [6]Pharm., Univ. Laval, Quebec, QC, Canada

Abstract: Alzheimer's disease (AD) remains an incurable, age-related neurocognitive disorder that is strongly linked to metabolic anomalies, including impaired insulin and glucose metabolism. The brown adipose tissue (BAT) plays a central role in body temperature regulation and energy balance and its activity start to deteriorate in the elderly around the same time as the incidence in AD rises. We previously showed that enhancing BAT activity improved glucose tolerance and recognition memory, but its effect on tau pathology was inconsistent. Here, we tested the hypothesis that activating β3AR located in the BAT mitigated cold-induced tau phosphorylation in a mouse model of AD. To that aim, we administered a β3AR agonist (CL,316-243, 1 mg/ kg, i.p.) for one-month to old NonTg and 3xTg-AD mice (n= 7-14/ group, age = 18 ± 0.2 months). At the end of treatment, while vehicle-treated mice were kept at 22°C, mice receiving either vehicle or the β3AR agonist CL,316-243, were exposed to an acute cold exposure (4°C, 24h). First, we confirmed that β3AR stimulation improved peripheral glucose and insulin metabolism in NonTg and 3xTg-AD. Treatment with the agonist led to weight loss of around 10%, lowered fasted glycemia levels (effect of treatment **$p<0.01$), and improved insulin sensitivity as assessed by insulin tolerance tests after three weeks of treatment (effect of treatment **$p<0.01$). In addition, increased temperature (rectal and tail) and uncoupling protein 1 (UCP1) relative levels in BAT homogenates were observed in mice that were treated with the agonist, confirming the effectiveness of CL,316-243 to stimulate thermogenesis. Chronic β3AR agonist administration almost fully prevented the rise in soluble pTau at epitopes pSer202 (CP13, 42%), pThr217 (17%) and pSer396/404 (PHF-1, 51%) induced by acute cold exposure in the hippocampus of 3xTg-AD mice. In parallel, CL,316-243 blunted cold-induced changes in kinases (phosphorylated GSK3β/ GSK3β) and phosphatases (methyl-PP2AC/ total protein) involved in the tau phosphorylation pathway but had limited effect on synaptic proteins. In conclusion, we show that a pharmacological stimulation of BAT thermogenesis protects from cold-induced hyperphosphorylation of tau in 3xTg-AD mice. These results further highlight the relevance of targeting β3AR in the BAT to prevent tau neuropathology in AD.

Disclosures: J. Valentin: None. **M. Tournissac:** None. **E. Planel:** None. **S.S. Hebert:** None. **C. Tremblay:** None. **F. Calon:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.09/B81

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

Support: NIH 1RF1AG077570

Title: Cortical pericyte activity dynamic changes during environmental stressors in murine model of Alzheimer

Authors: *Y. WU[1], M. LIU[2];
[1]Dept. of Psychiatry & Behavioral Sci., Med. Univ. of South Carolina, Charleston, SC;
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Abstract: As a significant component of the neurovascular unit (NVU) and blood-brain barrier (BBB), brain pericytes regulate cerebral blood flow and BBB permeability. Previous studies suggest that pericytes undergo degeneration in Alzheimer's disease (AD). However, the exact effects of AD pathology on pericyte functions remain unclear. Using the in vivo calcium imaging tool in freely moving mice, we recorded the activity dynamics of pericytes in the prefrontal cortex (PFC) of the transgenic AD mice expressing calcium (Ca^{2+}) indicator GCaMP6f in pericytes (5xFAD/Pdgfrb-iCre/GCaMP6f, FPG6) and control mice (Pdgfrb-iCre/GCaMP6f, PG6) under three environmental stressors: Tail suspension test (TST), Self-paced spontaneous exploration test in an open field (OF) and Elevated Plus Maze (EPM). The results showed that, during TST, PFC pericytes in both groups showed strong activation when mice were climbing and struggling while keeping silent when mice were immobile. However, the activation magnitude, manifested by the Ca^{2+} transient intensity, was significantly reduced in the FPG6 AD mice (Ca^{2+} transient changes: 0.29 in FPG6 versus 1.18 in PG6). Similarly, PFC pericytes in the PG6 mice exhibited significantly higher Ca^{2+} transient peak numbers in the open field than in the home cage (baseline). However, FPG6 mice showed no significant change in the Ca^{2+} transient peak number between the open field and the home cage (3.9 in FPG6 versus 5.9 in PG6). In the EPM test, pericytes from the PG6 mice showed significantly increased activities in the centre zone while pericytes from FPG6 mice did not. Our results first demonstrated that cortical pericytes undergo real-time activations upon environmental stresses, to which the response capability might be compromised in 5xFAD mice.

Disclosures: Y. Wu: None. **M. Liu:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.10/B82

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

Support: Arizona Biomedical Research Commission New Investigator Award #ADHS18-198875
R01DA052340

Title: Attenuation of Alzheimer's Disease-Driven Memory Loss, Dementia-Like Pain Behavior, and Loss of Thigmotaxis by Novel Isoform-Selective Heat Shock Protein 90-Beta Inhibitor Treatment in 5xFAD Mice

Authors: *B. D. K. GRATREAK[1], C. A. SEEKINS[2], T. D'AMICO[3], M. SERWETNYK[4], B. BLAGG[3], J. M. STREICHER[5];
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Abstract: Alzheimer's Disease (AD) is the most common cause of dementia and impacts over 6 million people in the United States. Its incidence grows with age, and therapeutics are urgently needed to halt disabling neuropsychological symptoms impacting patients and their families, notably, insidious memory loss. However, people with dementia also experience distressing levels of pain, thus understanding mechanisms driving pain in dementia is critically important in their care. Pain is the most shared symptom by more than half of patients with varying levels of dementia in their final week of life and 77% of patients with dementia rely on opioids for pain relief.
Here, we report the reversive arm of our studies to modify tightly evolutionarily conserved molecular chaperone protein networks that are closely tied to systemic immunological processes by selectively inhibiting a specific isoform of Heat Shock Protein 90 (Hsp90) in transgenic 5xFAD mice. Non-selective pan-Hsp90 inhibitors are robustly effective in treating AD via anti-inflammatory immune modulation of microglia signaling but were halted in clinical use by toxic side effects. Studies suggest toxicity of pan-Hsp90 inhibitors is driven mostly by effects of Hsp90α inhibition. Our lead compound is >333 fold selective for Hsp90β over Hsp90α and can selectively inhibit Hsp90β while skirting Hsp90α inhibition, thus we predict being able to achieve similar benefits with fewer side effects. We hypothesized that selective Hsp90β inhibition will reduce AD pathology in the 5xFAD mouse model by immune modulation, specifically by decreasing inflammatory microglial activation, and report immunohistochemical findings here. In addition, our previous studies show that Hsp90β-selective inhibition enhances morphine pain relief, a salient opioid dose-reducing bonus in this patient population.
Six-month-old female and male 5xFAD mice were treated daily by subcutaneous injection of our Hsp90β inhibitor NDNB-01 (1mg/kg) for nine weeks and tested with biweekly open field tests (OFT), novel object recognition (NOR) tests, and overnight nestbuilding assays and additional Morris Water Maze (MWM), tail flick, Hargreaves, and Elevated Plus Maze (EPM) testing. Our previous pilot data in younger mice suggested Hsp90β inhibition conferred a significant cognitive benefit in long-term 7-day retention NOR testing at thirteen weeks of treatment. Here, we describe effects in older 5xFAD mice with higher beta-amyloid loads, whereby Hsp90β inhibition enhanced 24-hr spatial memory in MWM, ameliorated cognitive changes in OFT and EPM, improved nest-building, and restored thermal nociception via Hargreaves testing.

Disclosures: B.D.K. Gratreak: None. **C.A. Seekins:** None. **T. D'Amico:** None. **M. Serwetnyk:** None. **B. blagg:** None. **J.M. Streicher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JMS is an equity holder in Teleport Pharmaceuticals, LLC, Botanical Results, LLC, but these companies are not Hsp90-related.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.11/B83

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

Support: NIH grant AT10980
NIH grant AG050431
VA merit award 1I01BX005002
VA merit award I01BX005613

Title: Balsam of Tolu/Peru component cinnamein binds to PPARα to reduce plaques and protect memory in a mouse model of AD

Authors: *K. PAHAN;
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Abstract: Despite intense investigations, no effective treatment is yet available to reduce plaques and protect memory and learning in patients with Alzheimer's disease (AD), the most common neurodegenerative disorder. Therefore, it is important to identify a non-toxic, but effective, treatment option for AD. This study highlights the importance of cinnamein, a component of balsam of Tolu/Peru, for decreasing plaques and improving cognitive functions in 5XFAD mouse model of AD. Oral administration of cinnamein led to significant reduction in amyloid-beta plaque deposits in the brain and protection of spatial learning and memory in 5XFAD mice. Peroxisome proliferator-activated receptor alpha (PPARα), a nuclear hormone receptor, is involved in plaque lowering and increase in hippocampal plasticity. While investigating underlying mechanisms using cheminformatics, thermal shift assays, and time-resolved fluorescence energy transfer (TR-FRET) analysis, we found that cinnamein served as a ligand of PPARα. Accordingly, oral cinnamein upregulated the level of PPARα, but not PPARβ, in the hippocampus, and remained unable to decrease plaques from the hippocampus and improve memory and learning in 5XFAD mice lacking PPARα. Finally, cinnamein treatment also upregulated the levels of ADAM10 (one of the drivers of nonamyloidogenic pathway) and TFEB (the master regulator of autophagy) in the brain of 5XFAD mice via PPARα. Collectively, our results suggest that this balsam component may have therapeutic importance in AD.

Disclosures: K. Pahan: None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.12/B84

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

Support: CSIR

Title: Sertad1 depletion using a lentiviral vector ameliorates cognitive dysfunction and synaptic deficits through autophagy modulation in 5xFAD transgenic mice model of Alzheimer's disease

Authors: *N. AMBAREEN[1,2], S. C. BISWAS[3];
[1]CSIR-Indian Inst. of Chem. Biol., Kolkata, India; [2]Acad. of Scientific and Innovative Res. (AcSIR), Ghaziabad- 201002, India; [3]CSIR-IICB, Kolkata, India

Abstract: The Alzheimer's disease (AD) brain is marked by accumulation of profuse electron dense autophagosomes due to impaired clearance by autophagy, exerting immense proteinopathic stress and neurotoxicity, whose mechanism remains unexplored. This study deciphers the role of Sertad1, a transcriptional coregulator, in dysfunctional autophagy in 5xFAD, familial AD transgenic mice model. We injected lentiviral particles expressing shSertad1 by bilateral stereotactic surgery in the hippocampal cornu ammonis1 (CA1) region of 5-month-old 5xFAD and control mice brain (n=7-10 mice per experimental group, male and female included). Statistical significance between two groups was done using two-tailed unpaired t-test and between more than two groups using one-way ANOVA. Data are represented as mean ± standard error of mean. Upon temporal profiling of autophagy proteins at 1, 3, 6 and 12 months of 5xFAD and control mice, we find significant autophagy induction in the cortical and hippocampal protein lysates of 5xFAD mice starting at 3 months compared to age-matched controls. Sertad1 is upregulated in 5xFAD mice cortex and hippocampus of age 1, 3, 6 and 12 months progressively as compared to age-matched control (C57BL6) mice. We show that Sertad1 knockdown lowers autophagy levels in 5xFAD mice cortex and hippocampus. Forkhead box protein O3 (FoxO3a) is a master regulator of the autophagy gene network. Interestingly, we observed that Sertad1 depletion not only blocks FoxO3a translocation to the nucleus in response to oligomeric Amyloid-β but also reduces its protein levels. Phosphorylation of FoxO3a responsible for its cytosolic retention is significantly restored in Sertad1 depleted 5xFAD mice. Akt is a negative upstream regulator of FoxO3a. We find that Akt activity is restored upon Sertad1 depletion in 5xFAD mice. Next, we performed cognitive tests including locomotion, fear conditioning, Morris Water Maze and Novel Object Recognition and find that Sertad1 depletion restores cognitive deficits in 5xFAD mice. Additionally, Sertad1 depletion restores pre and postsynaptic protein: SNAP25 and PSD95 levels, and dendritic spine density evident from Golgi-stained images of brain slices. Overall, dysfunctional autophagy occurs early in AD pathogenesis. Sertad1 is upregulated and mediates dysfunctional autophagy in AD mice through Akt/FoxO3a axis. Lentiviral delivery of shSertad1 particles can ameliorate behavioral deficits, promote autophagy flux and restore synaptic loss in 5xFAD mice. Through its multimodal regulation of autophagy-apoptosis cross-talk, we propose Sertad1 to be an excellent target for therapeutic intervention to combat AD.

Disclosures: N. Ambareen: None. **S.C. Biswas:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

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Program #/Poster #: PSTR107.13/B85

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

Support: IBRO exchange fellowship program - offered by International Brain Research Organization
Educational Grant (CAEN-1A) - offered by the International Society for Neurochemistry (ISN)
IUBMB Wood Whelan Research Fellowship - offered by The International Union of Biochemistry and Molecular Biology (IUBMB)
CAPEs PrInt travel grant

Title: Investigating the role of exercise linked-irisin and extracellular vesicles in Alzheimer's disease

Authors: *T. RODY SOUZA FERREIRA[1,2], N. M. LYRA E SILVA[3], T. HUNTER[3], G. B. DE FREITAS[4], C. FERNANDES[5], V. BODART-SANTOS[6], M. V. LOURENCO[7], S. T. FERREIRA[8], F. G. DE FELICE[9];
[1]Univ. Do Rio De Janeiro, Rio De Janeiro, Brazil; [2]Queen's University, Kingston, ON, Canada; [3]Queen's Univ., Kingston, ON, Canada; [4]Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada; [5]Inst. of Med. Biochem., Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil; [6]Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [7]Inst. of Med. Biochem. Leopoldo de Meis, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [8]Fed. Univ. Rio de Janeiro, Rio de Janeiro, Brazil; [9]Ctr. for Neurosci. Studies, Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by neurodegeneration, neuroinflammation, and memory loss. Due to the lack of disease-modifying treatments, the search for new therapeutic strategies for AD is necessary. Physical exercise has been investigated as a non-pharmacological therapy for AD. Preclinical studies demonstrate neuroprotective effects related to exercise in animal models of AD, such as learning and memory improvements. Exercise upregulates irisin, a myokine derived from fibronectin type III domain-containing protein 5 (FNDC5), previously shown by our group to promote cognitive improvements in AD models. Literature data suggest that increased FNDC5 / irisin signaling promotes cognitive improvements in AD models. Interestingly, the blockade of peripheral irisin prevented the neuroprotective effects of physical exercise on memory and synaptic plasticity, indicating that circulating irisin mediates the protective actions of exercise in the brain of AD mouse models. These findings suggest that enhancing brain irisin, through exercise or pharmacologically, may be beneficial in AD. Herein, we investigated extracellular vesicles

(EVs) as a therapeutic approach. EVs are membranous particles that play an important role in communication between the periphery and the brain, carrying biomolecules from donor to recipient cells, notably during exercise. We hypothesize that exercise stimulates irisin production (free and EVs) and EV-associated irisin reaches the brain, resulting in beneficial effects in cognition. Therefore, this study aims to investigate if EVs from mice carry FNDC5/irisin and the neuroprotective effect of an intravenous injection of an EV treatment. Our results show higher FNDC5/irisin concentrations in EV fractions of exercised mice in comparison to sedentary controls. Furthermore, EVs isolated from the plasma of exercised mice rescue memory impairments in AD mouse models. These findings indicate a therapeutic potential of EVs carrying irisin to restore cognition in AD.

Disclosures: T. Rody Souza Ferreira: None. **N.M. Lyra E Silva:** None. **T. Hunter:** None. **G.B. De Freitas:** None. **C. Fernandes:** None. **V. Bodart-Santos:** None. **M.V. Lourenco:** None. **S.T. Ferreira:** None. **F.G. De Felice:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.14/B86

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

Support: DFG DE 1536/12-1
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Franco-Bavarian University Cooperation Center under FK03-2020
Procope Mobility Program of the French Embassy in Germany
Campus France (PHC Procope)
German Academic Exchange Service (DAAD)
Federal Ministry of Education and Research (BMBF) project number 57702280

Title: The selective butyrylcholinesterase inhibitor UW-MD-95 shows symptomatic and neuroprotective effects in a pharmacological mouse model of Alzheimer's disease

Authors: A. CARLES[1], M. HOFFMANN[2], M. SCHEINER[2], L. CROUZIER[1], C. BERTRAND-GADAY[3], A. CHATONNET[3], M. DECKER[2], ***T. MAURICE**[1];
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Abstract: Alzheimer's disease (AD) is a devastating dementia characterized by extracellular amyloid-β (Aβ) protein aggregates and intracellular tau protein deposition. Clinically available drugs mainly target acetylcholinesterase (AChE) and indirectly sustain cholinergic neuronal tonus. Butyrylcholinesterase (BChE) also controls acetylcholine (ACh) turnover and is involved

in the formation of Aß aggregates and senile plaques. UW-MD-95 is a novel carbamate-based compound acting as a potent pseudo-irreversible BChE inhibitor, with high selectivity *vs* AChE, and showing promising protective potentials in AD. We characterized the neuroprotective activity of UW-MD-95 in mice treated intracerebroventricularly with oligomerized $A\beta_{25-35}$ peptide using behavioral, biochemical and immunohistochemical approaches. When injected acutely 30 min before the behavioral tests (spontaneous alternation in the Y-maze, object recognition or passive avoidance), UW-MD-95 (0.3-3 mg/kg) showed anti-amnesic effects in $A\beta_{25-35}$-treated mice. When injected once-a-day over 7 days, it prevented $A\beta_{25-35}$-induced memory deficits. This effect was lost in BChE knockout mice. Moreover, the compound prevented $A\beta_{25-35}$-induced oxidative stress (assessed by lipid peroxidation or cytochrome c release), neuroinflammation (IL-6 and TNFα levels or GFAP and IBA1 immunoreactivity) in the hippocampus and cortex, and apoptosis (Bax level). Moreover, UW-MD-95 significantly reduced the increase in soluble $A\beta_{1-42}$ level in the hippocampus induced by $A\beta_{25-35}$. UW-MD-95 appeared as a potent neuroprotective compound in the $A\beta_{25-35}$ model of AD, with potentially an impact on $A\beta_{1-42}$ accumulation that could suggest a novel mechanism of neuroprotection.

Disclosures: A. Carles: None. **M. Hoffmann:** None. **L. Crouzier:** None. **C. Bertrand-gaday:** None. **A. Chatonnet:** None. **M. Decker:** None. **T. Maurice:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.15/B87

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

Support: #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease

Title: A TRKA-biased optimized variant of human NGF with superior neuroprotective and anti-neurodegenerative activities in 5XFAD mice

Authors: A. TIBERI[1], F. MALERBA[2], R. FLORIO[2], G. BORGONOVO[1], E. COULOMB[1], M. CALVELLO[1], V. GAZZANO[3], ***S. CAPSONI**[4,5], A. CATTANEO[2,5];
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Abstract: The delivery of Nerve Growth Factor (NGF) to the brain in a safe and long-term manner, limiting the adverse effects of NGF in activating nociceptive responses, has represented a significant challenge, due to the limited access of the protein to the brain and to peripheral nociceptive properties. To overcome these limits our laboratory undertook a two-tier approach:

an intranasal delivery coupled to the development of painless NGF (pNGF), an optimized form of human NGF, devoid of p75NTR binding and signalling, with a 10-fold reduced pain-triggering activity. The aim of this study was to perform a head-to-head comparison of the anti-neurodegenerative properties of pNGF with respect to those of wildtype NGF (wtNGF). We first compared the biodistribution of wtNGF and pNGF in the cerebral cortex after intranasal delivery in WT mice. We found that 12 hours after the administration the amount of pNGF is higher than the one detected for wtNGF. Then, both neurotrophins were administered intranasally to 3-months old 5xFAD mice every other day for 3 weeks at the dose of 0.54 microg/kg, followed by one week of washout. At end of this period, mice were analyzed to explore the efficacy of the treatments on memory deficit, APP processing, β-amyloid deposition, and cytokine expression in the brain. We found that both neurotrophins rescue memory deficits and increase cholinergic sprouting. However, only pNGF determined a significant decrease of Aβ production and deposition, due to a reduction in the expression of γ and β-secretases, and a selective modulation of cytokines. wtNGF did not rescue β-amyloid deposition and β-secretase expression. After wtNGF treatment, microglia ramifications remained shorted as in 5xFAD mice treated with vehicle. On the contrary, pNGF increased the length of microglia ramifications to an extent like WT microglia. Moreover, wtNGF increased TNFα brain bioavailability, which was decreased by pNGF. Thus, we found that pNGF is characterized by a more potent neuroprotective profile that wtNGF, making it a better therapeutic candidate for the treatment neurodegenerative diseases.

Disclosures: A. Tiberi: None. **F. Malerba:** None. **R. Florio:** None. **G. Borgonovo:** None. **E. Coulomb:** None. **M. Calvello:** None. **V. Gazzano:** None. **S. Capsoni:** None. **A. Cattaneo:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.16/B88

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

Support: Ministry of Science and Technology (MOST), Taiwan (MOST-110-2410-H-320-004-MY2)
Buddhist Tzu Chi Medical Foundation (TCMF-SP 108-04)

Title: Tcu431 confers neuroprotective effects against amyloid-beta toxicity in ht22 cells and rescues memory deficits in 3xtg-ad mice

Authors: *A. IBIAYO, I. LIU;
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Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the gradual deterioration of brain cells, characterized by neuroinflammation and memory loss. TCU431, an herbal medicine, has been observed to possess anti-inflammatory

properties, enhance memory function, and exhibit neuroprotective effects. This study aims to determine the cellular role of TCU431 on HT22 mouse hippocampal cell line and examine its therapeutic potential against neuroinflammation, synaptic dysfunction, and memory deficits in the triple transgenic Alzheimer's disease (3xTg-AD) mice.**Methods:** MTT assay was utilized to assess the cellular effect of TCU431 and its co-treatment with amyloid beta oligomers on HT22 cells after 24 and 48 hours. Then, the expression of NF-κB was measured by immunofluorescence staining. For the *in vivo* study, TCU431 was administered at 200 mg/kg via oral gavage for 18 consecutive days to 6-month-old female 3xTg-AD mice. Western blot assay was used to determine the levels of p-synapsin 1, synapsin 1, PSD95, BDNF/TrkB, and pERK/ERK molecules. The open field, T-maze, and Morris water maze tests were used to evaluate locomotion activity, working memory, and spatial reversal memory, respectively. **Results**: At concentrations of 5 µg/ml and 20 µg/ml, TCU431 preserved neuronal cell viability, conferred neuroprotection against amyloid beta-induced cytotoxicity, and attenuated the NF-κB inflammatory expression in the HT22 cells. Notably, significant improvements were observed in the 3xTg-AD mice treated with 200 mg/kg of TCU431 in both working and spatial reversal memory deficits. Additionally, TCU431 significantly reversed the altered levels of p-synapsin 1, synapsin 1, PSD95, BDNF/TrkB, and pERK/ERK molecules in the treated 3xTg-AD mice.**Conclusion:** These findings show that TCU431 holds promising potential as a therapeutic herbal medicine for mitigating AD symptoms, including neuroinflammation, synaptic dysfunction, and memory deficit.

Disclosures: A. Ibiayo: None. **I. Liu:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.17/B89

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

Support: NIH NINDS R01 NS073899
Alzheimer's Assocaition AARG-22-974562

Title: Fkbp51 inhibition: a potential therapy to improve resilience in the tauopathic brain?

Authors: *A. CONTRERAS-MARCIALES[1,2], D. MEZQUITE-GARCIA[1,2], L. VERDINA[1,2], S. E. HILL[1,2], L. J. BLAIR[1,3,2];
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Abstract: Tau protein aggregates in the brain are the primary feature in a group of progressive neurodegenerative disorders known as Tauopathies, the most common being Alzheimer's disease (AD). In human AD brain tissue, the 51 kDa FK506-binding protein (FKBP51, encoded by *FKBP5*), a co-chaperone of the Hsp90 complex involved in stress response regulation, is

upregulated. Our lab demonstrated that FKBP51 overexpression in a tau transgenic mouse model promoted the accumulation of toxic tau oligomers. We and others have also showed lower phosphorylated and total tau in FKBP51 KOs compared to wild type (WT) mice. Based on this, we hypothesize that inhibition of FKBP51 will provide resilience in the brains of tau transgenic mice. To test this, we evaluated the effects of a pharmacological inhibitor of FKBP51, SAFit2, on tau levels and cognitive activity in PS19 tau transgenic mice. Male and female 7.5-month-old PS19 and WT mice were i.p. injected twice a day for 28 days with 10 mg/kg of SAFit2 or vehicle (n = 12 mice/treatment/genotype/sex). Two weeks into the treatment, blood serum was collected before and after acute tube restraint stress, which will be assessed by ELISA to measure the potential protective effects of SAFit2 on corticosterone levels after stress, as reported in other models. The final week of treatment, behavioral tests were performed for cognition and affective-like behaviors including the Open Field Test, Novel Object Recognition, Tail Suspension Test, and Radial Arm Water Maze with Reversal. On the last day, brain tissue and blood serum were collected 1 hour after the final treatment. Behavioral and tissue analyses are currently ongoing. According to our preliminary data, we expect to find that chronic SAFit2 treatment induces stress-resilience and lowers phospho- and total tau levels and possibly FKBP51 levels. We also expect to see a concomitant improvement in cognitive skills of SAFit2-treated mice compared to vehicle-treated PS19 mice, while no changes are expected in the WT littermate controls. This study will help clarify the role of FKBP51 inhibition as a possible therapeutic intervention for the treatment of tauopathies.

Disclosures: A. Contreras-Marciales: None. **D. Mezquite-Garcia:** None. **L. Verdina:** None. **S.E. Hill:** None. **L.J. Blair:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.18/B90

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

Support: A Long Swim for ALS

Title: A Novel Reporter Mouse Model Providing Insights into Neuroinflammatory Modulation of Upper Motor Neurons within the Context of TDP-43 Pathology

Authors: *E. ULUPINAR[1], C. SILVA SOARES[1], Z. Y. EROL[1], A. AHRENS[1], P. OZDINLER[1,2,3,4];
[1]Neurol., [2]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., [3]Robert H. Lurie Comprehensive Cancer Ctr., Northwestern Univ., Chicago, IL; [4]Les Turner ALS Ctr., Chicago, IL

Abstract: Protein aggregation and neuroinflammation are two common features in numerous neurodegenerative diseases. Transgenic mice expressing the human disease-causing TAR DNA

binding protein-43 mutation (TDP-43^{A315T}) are invaluable tool for studying frontotemporal degeneration (FTD) and amyotrophic lateral sclerosis (ALS). However, the role of peripheral or innate immune cells in cortical degeneration, especially the degeneration of the upper motor neurons (UMNs), remains unknown. In this study, we aimed to bridge this gap by developing a novel transgenic mouse model, in which the UMNs as well as the cells that are important for the initiation of the innate immune system are fluorescently labeled. We took advantage of UCHL1-eGFP reporter mice to specifically label corticospinal motor neurons (CSMN, a.k.a UMNs in mice) and crossed them with monocyte chemoattractant protein-1 (MCP1)-monomeric red fluorescent protein-1 (mRFP) reporter line, thereby creating a double transgenic reporter mouse model. Subsequently, we introduced prpTDP-43^{A315T} transgenic mice into this double transgenic to generate a triple transgenic mice, in which MCP1-positive cells and CSMN are fluorescently labeled within the context of TDP-43 pathology. This transgenic line allows cellular visualization of both the key cells of the innate immune system as well as the motor neurons that degenerate in ALS and ALS/FTD. This significant shift from mice to neuron/cell enables more direct and translational analyses of the cellular defects observed in ALS and ALS/FTD patients with TDP-43 pathology. We conducted immunocytochemical analyses on paraformaldehyde fixed brain sections of both healthy and diseased animals at postnatal days 30, 60, and 100 (n=4 per group, per time point). Our results begin to reveal the intricate encounters of MCP1-positive cells with CSMN that become vulnerable and display progressive degeneration over time. We can, now, visualize how, when and where they interact at a cellular level. Flow cytometry analyses are also beginning to reveal dynamic changes on the identity of cells that express MCP1 and how they differ between periphery and the CNS. Our study provides compelling evidence of enhanced MCP1 expression and microglia-CSMN interactions in with respect to disease, emphasizing the significance of early neuroinflammatory influences in TDP-43 pathology. This novel triple transgenic mouse model offers cellular clarity on the complex cellular dynamics of neuroimmune modulation in TDP-43 pathology, providing insights directly relevant to human ALS and ALS/FTD patients.

Disclosures: E. Ulupinar: None. **C. Silva Soares:** None. **Z.Y. Erol:** None. **A. Ahrens:** None. **P. Ozdinler:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.19/B91

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

Support: P01AG060882
R01AG072507
K99AG073507
Brain & Behavior Research Foundation Grant ID 30397
P30AG066512

Title: Acute Aβ12-28P administration targeting the apoE4/Aβ interaction rescues advanced-stage Alzheimer's disease

Authors: *T. NGUYEN[1], K. HA[1], Y. XU[1], N. LAM[1], Z. LI[1], P. LIU[1], Z. SUN[1], J. KAMB[1], C. KIM[1], A. V. MASURKAR[2], S. CHEN[3], T. M. WISNIEWSKI[1];
[1]NYU Grossman Sch. of Med., New York, NY; [2]NYU Grossman Sch. of Med., New York, NY, ; [3]New York University, Sch. of Med., New York, NY.

Abstract: Apolipoprotein E4 (apoE4) has been identified as the major genetic risk factor for late onset Alzheimer's disease (AD). Our lab has demonstrated that chronic administration of Aβ12-28P, a synthetic peptide that blocks apoE4/Aβ binding, in middle-aged transgenic AD mice significantly ameliorates pathology progression, resulting in reduced Aβ plaques deposition and cerebral amyloid angiopathy along with improved memory and cognition. However, whether blocking apoE4/Aβ interaction by Aβ12-28P also has an ameliorating effect on the neuronal and cognitive function of old AD mice where Aβ pathology is advanced remains unknown. We therefore treated geriatric SwDI/APOE4 mice (18-24 months old) with daily intraperitoneal injection of Aβ12-28P. Behavioral tests were performed 2 hours post-injection to assess the acute cognitive effect of Aβ12-28P. Acute Aβ12-28P treatment resulted in significant cognitive improvement. While the treated mice did not show differences in locomotor activity, significantly enhanced cognitive performance was observed, including improved performance in one-day T-maze test, one-day novel object recognition test, and multiple-days radial arm maze testing. Aβ12-28P administration also significantly reduced anxiety in open field testing. After 3 weeks of behavioral testing with daily treatment, acute hippocampal slices were prepared and subjected to *in vitro* physiology experiments to evaluate long-term potentiation (LTP) of Schaffer collateral input to CA1. On the recording day Aβ12-28P or saline was injected 2 hours before slice preparation. Slices from the treated animals showed significantly enhanced LTP, suggesting rescued synaptic plasticity. These results suggest that acute Aβ12-28P administration blocking apoE/Aβ binding rescues synaptic plasticity and cognitive decline in old AD mice where extensive Aβ pathology has been developed. Our findings opens the possibility of applying our strategy of targeting the apoE/Aβ interaction for alleviating advanced-stage AD symptoms in patients.

Disclosures: T. Nguyen: None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.20/Web Only

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

Support: P01AG026572
R01AG057931

Title: Neurodegenerative Disease Genetics Display Antagonistic Pleiotropy in Mouse Colony Fertility

Authors: *L. CAMPBELL[1], A. DALTON[1], T. STANLEY[1], M. SCHWAB[1], J.-P. WIEGAND[1], E. REYES-REYES[2], K. RODGERS[1], R. D. BRINTON[1];
[1]Ctr. for Innovation in Brain Sci., Univ. of Arizona, Tucson, AZ; [2]UAHS Brain Sci., Univ. of Arizona, Tucson, AZ

Abstract: Background: Antagonistic pleiotropy describes genetics that provide early benefits to species survival and reproduction at the cost of deficits in the post-reproductive age. Neurodegenerative disease risk genetics adversely affect aged, neuronal function but it is largely unknown how they affect species survival and fertility. Here we investigate the most prevalent genetic bases for prominent neurodegenerative diseases, such as Alzheimer's Disease (hAPP and hAPOE4), Parkinson's Disease (GBA1-L444P), and Multiple Sclerosis (HLA-DRB2*1501), and their effect on litter number, size, and clinical observations. Method: Transgenic mice carrying hAPOE alleles (JAX#27894, APOE3/3 KI, https://www.jax.org/strain/027894 and JAX#29018, APOE4/4 KI, https://www.jax.org/strain/029018) were obtained and bred. APOE KI mice were subsequently bred to homozygous B6(SJL)-App tm1.1Aduci/J animals (JAX#030898, hAbeta-loxP-KI). Heterozygous and wild-type GBA-L444P mice were obtained (MMRRC#000117-UNC) and cross-bred. HLA-DRB2*1501 mice were obtained (Vandenbark Lab, OHSU) and each breeder pair was phenotyped for low (<5%) MHC expression and high (>75%) HLA expression. Mice were longitudinally tracked for identification, weighed monthly, and observed for clinical observations, breeding characteristics, and survival rates. Results: Colony-wide analyses indicated in two key differences: 1) HLA-DRB2*1501 carriers displayed the lowest fertility as measured by average number of litters per breeder and average litter size. 2) GBA-L444P displayed the most antagonistic pleiotropy, with the highest average litter size of 8.6 pups and number of litters. Conclusion: According to the Jackson Laboratory Resource Manual Breeding Strategies for Maintaining Colonies of Laboratory Mice (http://ko.cwru.edu/info/breeding_strategies_manual.pdf), mean size of litters in the C57BL/6 and DBA/2 parental strains is 4.9 and 4.7 pups. This suggests that all genetics, except for HLA-DRB2*1501 display antagonistic pleiotropy: increased litter size, at the risk of neurodegenerative disease. class="MsoNormal" style="margin: 0in; font-size: 12pt; font-family: Calibri, sans-serif;">

Disclosures: L. Campbell: None. **A. Dalton:** None. **T. Stanley:** None. **M. Schwab:** None. **J. Wiegand:** None. **E. Reyes-Reyes:** None. **K. Rodgers:** None. **R.D. Brinton:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.21/B92

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

Support: NIH NIA R01AG068330
BrightFocus Foundation A20201775S
T32NS115704
F31AG066302
P30GM127211
P20GM148326

Title: Metformin reduces amyloid plaque burden and rescues sleep and metabolism in APP/PS1 mice

Authors: *C. C. ASHLEY[1], N. J. CONSTANTINO[2], R. E. IRMEN[2], C. M. CARROLL[3], A. SNIPES[2], S. L. MACAULEY[2];
[1]Univ. of Kentucky, Lexington, KY; [2]Physiol., Univ. of Kentucky, Lexington, KY; [3]Psychiatry, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Alzheimer's Disease (AD), the most common cause of dementia, is a progressive neurodegenerative disorder characterized by amyloid-beta (Aβ) plaques and subsequent aggregation of hyperphosphorylated tau and cognitive decline. AD also includes complex inflammatory, vascular, metabolic, and sleep pathologies. Previous research has shown that Aβ, metabolism, and sleep are bidirectionally interrelated. Our lab previously demonstrated that Aβ plaques not only cause glucose intolerance but also alter the brain's response to a metabolic challenge. Amyloid plaques also flatten diurnal rhythms of interstitial fluid (ISF) lactate, which correlates with decreased slow wave NREM sleep. This raises the question as to whether targeting glucose metabolism in an APP/PS1 mouse model of Aβ overexpression will rescue metabolic and sleep deficits. Metformin is a first-line treatment for Type-2-diabetes known to reduce hepatic glucose production and restore glucose tolerance. There is emerging evidence for its potential role as a novel therapeutic in a variety of other diseases, including AD. Metformin's exact mechanism of action, however, is not fully understood, and no studies thus far have looked at its impact in the context of sleep, metabolism, and Aβ pathology. Therefore, our lab investigated whether metformin treatment restores metabolic deficits in APP/PS1 mice and rescues sleep loss. Metformin dissolved in drinking water (300mg/kg) was administered to 6-month-old APP/PS1 female mice at both an acute (1 week, n = 6-8) and chronic (3 months, n = 8) timepoint. Control mice, including APP/PS1 (n = 9) and wildtype females (n = 10), received regular drinking water. EEG/EMG electrodes and metabolite-specific biosensors were placed in the brain to record sleep/wake activity and fluctuations in brain ISF glucose and lactate, respectively. Mice were then euthanized, transcardially perfused, and brains dissected for post-mortem analysis. Acute metformin treatment restored ISF glucose and lactate rhythms, glucose tolerance, and slow wave sleep activity, indicating that acute treatment can rescue metabolism and sleep deficits in APP/PS1 mice. In our chronic studies, Aβ (HJ3.4B) staining was performed to assess Aβ deposition in response to metformin treatment. Chronic metformin treatment significantly reduced Aβ deposition, plaque size, and plaque number in APP/PS1 mice compared to untreated controls. Ongoing studies are investigating whether reductions in amyloid plaques correlates with sleep improvement. Together, these results suggest that metformin treatment can reverse sleep and metabolism dysfunction due to Aβ pathology in mice.

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Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.22/B93

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

Support: NIH Grant R01 DC 019348
NSF Grant IOS 1652432

Title: Longitudinal analysis of behavior and neuropathology in a mouse model of Alzheimer's disease.

Authors: *K. W. I. NOUROZI[1], W. SITTERSON[2], I. LIM[1], C. C. LEE[3];
[1]Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA; [2]Sch. of Vet. Med., Louisiana State Univ., Baton Rouge, LA; [3]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: Alzheimer's disease is one of the most common forms of dementia. It is marked by degeneration of both neurons and glial cells, the formation of amyloid plaques, and disruptions in the brain's cholinergic systems. Its manifestations include compromised cognitive abilities, memory impairment, alterations in visuospatial skills, personality shifts, and depression. The onset and progression of Alzheimer's disease is influenced by numerous factors, such as age, genetics, brain and vascular trauma, infections, and environmental triggers. Numerous therapeutic approaches address symptoms linked to Alzheimer's disease, and recent research indicates that N-methyl-D-aspartate (NMDA) receptor antagonists like ketamine may offer neuroprotective benefits along with a reduction in neuropsychiatric symptoms. Notably, ketamine shows promise in potentially safeguarding neurons, glial cells, and astrocytes, offering therapeutic advantages and potentially delaying symptom onset. Therefore, we explored the potential neuroprotective advantages of early, low-dose administration of ketamine in a mouse model of familial Alzheimer's Disease. Animals were assessed behaviorally and neuroanatomically longitudinally for several months following treatment. Behavioral assessments included the novel object recognition, Y maze, and forced swim tests. Neuropathological examination of brain specimens was used to assess neurodegenerative alterations and amyloid plaque formation. As a result of these studies, we established and validated a pre-clinical framework for the longitudinal analysis of therapeutic potential for Alzheimer's disease and related dementias, which can inform future studies of the disorder.

Disclosures: K.W.I. Nourozi: None. **W. Sitterson:** None. **I. Lim:** None. **C.C. Lee:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.23/B94

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

Title: Preclinical efficacy of KGC's natural product, G1899, in mouse model of Alzheimer's disease

Authors: *S. KWEON[1], J. LEE[2], B. HAN[2], H. KO[1];
[1]Inst. for Cell Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]The Korean Ginseng Res. Inst., Korea Ginseng Corp., Gwacheon-si, Gyeonggi-do, Korea, Republic of

Abstract: Preclinical research on Korean Red Ginseng (KRG) extracts suggests potential benefits for anti-aging and Alzheimer's disease (AD), which has prompted us to investigate American ginseng extracts as another potential treatment option for AD. Therefore, the main purpose of this study is to examine the effect of G1899 (American ginseng, Panax quinquefolius), an herbaceous perennial plant in the ivy family native to eastern North America, newly standardized by Korea Ginseng Corporation (KGC, Korea), in the context of neuroprotection. Ginsenosides found in American ginseng possess antioxidant, anti-inflammatory, and neuroprotective properties, making them suitable for neurodegenerative studies. Given the growing prevalence of AD, exploring American ginseng's benefits on life expectancy and AD is crucial. Rigorous research, including preclinical and clinical trials, is needed to evaluate efficacy and dosage as a dietary supplement in daily life. Positive outcomes could enhance the well-being and anti-aging effect on individuals as well as AD patients. To assess G1899's neuroprotective effects, neurons were treated with glutamate or amyloid beta oligomer (Aβo) along with G1899. Several cell viability assays confirmed G1899's neuroprotective effect on inhibiting cell death and increasing cell survival rates. Additional experiments regarding the neuroinflammatory signaling pathway in microglia were conducted. We also examined Aβo's impact on microglia, which plays a pivotal role in CNS neuroinflammation. G1899 treatment increased beneficial microglial activation markers like TMEM119 and CD68 while alleviating the detrimental reactive status of microglia. Moreover, G1899 reduced NLRP3-mediated inflammasome formation induced by Aβo. To further evaluate G1899's efficacy in mitigating cognitive impairment induced by Scopolamine (SCP) in vivo, a fear conditioning test for determining learning and memory-based cognitive deficits was conducted and SCP-induced cognitive impairment was rescued by G1899 treatment.

Disclosures: S. Kweon: None. **J. Lee:** None. **B. han:** None. **H. Ko:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.24/B95

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

Support: NII core grant
DBT grant

Title: Dissecting the role of miRNA in Cell cycle Related Neuronal Apoptosis (CRNA)

Authors: *K. SINGH[1,2], M. CHAUHAN[3], C. CHONGTHAM[2], A. ARIMBASSERI[2], P. SHARMA[2];
[1]Jawaharlal Nehru Univ., New Delhi, India; [2]Natl. Inst. of Immunol., New Delhi, India; [3]Natl. Inst. of Immunol., Minneapolis, MN.

Abstract: Aberrant activation of the cell cycle of terminally-differentiated neurons results in their apoptosis and is known to contribute to neuronal loss in various neurodegenerative disorders like Alzheimer's Disease (AD). However, the mechanisms that regulate Cell Cycle Related Neuronal Apoptosis (CRNA) are poorly understood. It is important to know how cell cycle related genes are up regulated in this situation. While miRNA are implicated in the process of cell cycle regulation but their correlation with the neuronal cell cycle regulation and neuronal loss has remained unknown. We have used APP/PS1 transgenic mouse model for AD (TgAD) and cultured cortical neurons to study CRNA, which was evaluated by assessing levels of cell cycle and apoptotic markers. RNAseq was performed to identify miRNA deregulated in AD model, which was validated by qRT-PCR. Deregulation of miRNA that target cell cycle related genes was observed in TgAD neurons. Investigations on two of these miRNA (miR-449a and miR-16-5p) revealed that they suppress the cell cycle during neuronal differentiation. In response to neurotoxic amyloid peptide $A\beta_{42}$, their expression was impaired, which contributed to Cell cycle Related Neuronal Apoptosis (CRNA). Molecular mechanisms via which these miRNA are deregulated, which in turn may contribute to CRNA, were also deciphered. Importantly, the overexpression of these miRNA can improve memory and learning in TgAD mice and also revert neuronal cell death.

Disclosures: K. Singh: None. **M. Chauhan:** None. **C. Chongtham:** None. **A. Arimbasseri:** None. **P. Sharma:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.25/Web Only

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

Support: AARG-17-533363
NIA R21 – AG059223
NIA R01 – AG063945

Title: Longitudinal Effects of PLD1 Inhibitor, VU0155069 on Transgenic Alzheimer’s Disease Animal Mouse Model.

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Abstract: Background: Alzheimer's disease (AD) is the 5th leading cause of death in the United States. AD is a neurodegenerative disorder characterized by progressive loss of memory. The two hallmarks of the disease include Abeta (Aβ) and tau. We reported a key role for aberrantly elevated phospholipase D1 (PLD1) as a sufficient factor in driving the synaptic dysfunction and underlying memory deficits associated with progressive accumulation of Aβ and tau in the 3xTg-AD mouse model. Phospholipase D is a family of lipolytic enzymes that predominantly breaks down membrane phospholipids into phosphatidic acid and choline. There are two mammalian isoforms of the phosphatidylcholine (PC)-specific PLD - PC-PLD1 and PC-PLD2. Due to its conserved status, PLD participates in numerous signaling pathways and protein-protein interactions which are involved with, among other pathways, in synaptic neurotransmission and dendritic spine integrity. Our group demonstrated an essential role for PLD isoforms in the acquisition and expression of amygdala-associativememory in the adult rat. PLD1 is required for normal functioning, however, aberrantly elevated expression of PLD1 in the human post-mortem brains and the 3xTg-AD model suggest that post-developmental regulation of PLD levels and activity is key to healthy aging including synaptic function. **In the present study,** we demonstrate that reducing the levels of PLD1 in the 3xTgAD mice model of 6-, 12- and 18-months shows an improvement in the behavior as well as synaptic memory of the mice. This reduction is induced by giving a low dose of the VU0155069 compound to the mice at 5-, 11-, and 17-months of age intraperitoneally for one month, every alternate day. VU0155069 is a specific PLD1 inhibitor, and the dosage regimen given to the mice is 1 mg/kg. The longitudinal effects of PLD1 attenuation on signaling pathways important for synaptic resilience and dendritic spine integrity will be discussed. **Methods:** Western blotting, electrophysiology, behavior, FASS-LTP, immunofluorescence.

Disclosures: S. Budhwani: None. **S. Sreenivasa murthy:** None. **C. Natarajan:** None. **K. Garza:** None. **B. Krishnan:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.26/B96

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

Support: JPB grant MR-2023-4260
HHMI

Title: Tyk2: a critical regulator of tau levels, phosphorylation, and aggregation in tauopathy

Authors: *J. KIM[1,2], B. TADROS[1,2], Y. WEI[1,2], Y. KIM[3,2], C. A. LASAGNA-REEVES[4], D.-E. C. CHUNG[1,2], D. M. HOLTZMAN[5], B. HYMAN[6], H. Y. ZOGHBI[1,2,7,8];
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Abstract: Currently, more than 26 different tauopathies have been identified including Alzheimer's disease (AD) and Parkinson's disease (PD), in each case of which displays the distinct clinical and pathophysiological features. Despite this heterogeneity, all tauopathies are characterized by neuronal and/or glial tau-positive inclusion in the brain. Even though there is a common phenomenon of the accumulated pathogenic tau species as well as total in all tauopathies, however, how pathogenic cascade of tau protein from soluble to NF is mostly uncovered yet.Given the notion that the level of tau protein is one of the major determining factors of disease initiation and progression, our prior study identified TYK2 as a potential regulator of tau level in which TYK2 knockdown by siRNA reduced endogenous tau level in human cell.TYK2 is a tyrosine kinase which and a member of Janus kinases (JAKs) protein family, and associates with the cytoplasmic domain of type I and type II cytokine receptors promulgating cytokine signals by phosphorylating receptor subunits.In this study, we hypothesized that TYK2 is an important regulator of not only tau level but also pathogenesis of tau via phosphorylation of tau protein. Thought the series biochemical experiments, we discovered TYK2 phosphorylated tau protein at tyrosine 29 residue (Y29) and stabilized tau protein in human cells and mouse primary cultured neurons. Notably, TYK2 enhanced the forming aggregation of pathogenic tau (tau441_P301S) but not tau441_Y29F_P301S, phosphorylation insensitive mutation at Y29. Interestingly, tau phosphorylation at Y29 by TYK2 also facilitate nitration at same residue which is relevant to tauopathies in human patients. Tau441_Y29F_P301S displayed the reduced pathogenic phosphorylated tau species comparing to tau441P301S in mouse brain. To determine the potential benefit of the TYK2 intervention *in vivo,* we knocked down TYK2 gene using shRNA delivered by intracerebroventricular injection of AAV in P301S transgenic mouse, PS19 line. The knockdown of TYK2 reduced number of pathogenic specie of tau protein including phosphorylated tau as well as total tau protein.Collectively, these data suggest that Partial inhibition of TYK2 could thus be a strategy to reduce tau levels and toxicity

Disclosures: J. Kim: None. **B. Tadros:** None. **Y. Wei:** None. **Y. Kim:** None. **C.A. Lasagna-Reeves:** None. **D.C. Chung:** None. **D.M. Holtzman:** None. **B. Hyman:** None. **H.Y. Zoghbi:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.27/B97

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

Support: BIOCODEX Foundation (FRANCE)
Alzheimer´s Association (USA)

Title: Regulation of estrogen levels by the gut microbiota in a murine model of Alzheimer's disease

Authors: *I. S. ROMERO[1], J. GARCÍA-MENA[2], C. PEREZ-CRUZ[3];
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Abstract: Background: Alzheimer´s disease (AD) is the most common type of dementia, affecting more than 50 million people Worldwide. Epidemiological data indicate that women are the sector most affected since they represent almost two-thirds of patients diagnosed with AD [1]. One major sex difference heralded by pre-clinical and human studies is the menopause transition. During aging women suffer a gradual depletion of estrogen production, a hormone associated with better cognitive function [2]. On the other hand, recent studies highlight the role of gut microbiota (GM) in AD pathogenesis, as subjects suffering from AD present intestinal dysbiosis [3]. In this study, we aimed to assess GM alterations and estradiol (E2) levels in a transgenic animal model of AD. **Methods and results:** Six months-old female APP/PS1 (TG) and their Wild-type littermates (WT) were used for this study. A second group of animals received antibiotics during one-month before sacrifice to deplete the GM (TG-Abx; WT-Abx). Fecal and serum samples were collected to determine the composition of GM through DNA sequencing and bioinformatics analyses; E2 levels and enzymatic activity of beta-glucuronidase (b-GUS) were assessed by ELISA assay. We observed that TG mice have a greater fecal / plasma ratio of E2 compared to WT mice. The greater E2 excretion was associated with a different GM composition, as a lower abundance of bacteria carrying b-GUS was observed in TG mice. Antibiotic-treatment disrupts the fecal/plasma ration in WT mice, indicating that GM dysbiosis leads to lower E2 levels in the circulation. **Conclusion:** These data contribute to the understanding of factors that may increase the risk of developing dementia in females.
References: [1] Li, R., Cui, J., & Shen, Y. (2014). Brain sex matters: estrogen in cognition and Alzheimer’s disease. Molecular and cellular endocrinology, 389(1-2), 13-21; [2] Ervin, S. M., Li, H., Lim, L., Roberts, L. R., Liang, X., Mani, S., & Redinbo, M. R. (2019). Gut microbial β-glucuronidases reactivate estrogens as components of the estrobolome that reactivate estrogens. Journal of Biological Chemistry, 294(49), 18586-18599; [3] Jiang C, Li G, Huang P, Liu Z, Zhao B. The Gut Microbiota and Alzheimer's Disease. J Alzheimers Dis. 2017;58(1):1-15; [4] Cuervo-Zanatta D, Garcia-Mena J, Perez-Cruz C. Gut Microbiota Alterations and Cognitive Impairment Are Sexually Dissociated in a Transgenic Mice Model of Alzheimer's Disease. J Alzheimers Dis. 2021;82(s1):S195- S214.

Disclosures: I.S. Romero: None. **J. García-Mena:** None. **C. Perez-Cruz:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.28/B98

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

Title: Gender Differences in Alzheimer's Disease Progression and Cognitive Function in 5xFAD Mice.

Authors: *J. LEE, K. PARK, S. LEE, Y. KIM, Y. KANG, A. LEE, T. KIM, S.-Y. NA, P. J. SWEENEY, L. PARK;
Naason Sci., Cheongju-si, Korea, Republic of

Abstract: To understand Alzheimer's disease (AD) progression, reliable animal models are crucial. One such widely utilized model is the 5xFAD mice, engineered to express human APP and PSEN1 transgenes bearing five AD-linked mutations. While this model is important for studying AD, discrepancies in research findings underscores the necessity of acknowledging gender differences in disease manifestation. In both clinical and preclinical research, females are often excluded due to potential pregnancy or hormonal fluctuations. Nevertheless, AD is more prevalent in women, affecting 7.1% compared to 3.3% in men. Despite this gender disparity, preclinical studies frequently use only male mice, primarily due to financial constraints. This study focuses on investigating gender-specific differences in disease onset and progression in 5xFAD mice, examining amyloid-beta (Aβ) accumulation, inflammatory responses, neurofilament light (NF-L) variations, and cognitive-behavioral functions. The study found that female 5xFAD mice showed elevated Aβ levels and increased inflammation in the cortex and hippocampus compared to males. Cognitive assessments revealed that differences in cognitive function between wild-type (WT) and transgenic (TG) female mice were more pronounced between 9 and 12 months of age compared to male counterparts. Cognitive disparities were observed as early as 6 months in the Morris Water Maze (MWM) test, while the Y-maze (YM) and novel object recognition (NOR) tests showed significant differences from 9 months onward. Aβ deposition in the cortex and hippocampus began at 3 months, paralleling NF-L variations in cerebrospinal fluid (CSF) that differentiated WT and TG mice starting at 3 months, reaching a peak at 12 months. Immunohistochemistry disclosed the presence of Aβ in 5xFAD mouse brains from 3 months onward, accompanied by inflammation markers such as GFAP and Iba-1. Gender-specific cognitive-behavioral assessments showed faster disease progression in females, marked by higher Aβ levels and earlier disease onset compared to males. NF-L measurements in CSF indicated neuronal death due to Aβ accumulation, with greater differences in females than males at 3 months, with noticeable differences in both sexes from 6 months onwards. Therefore, considering gender disparities is crucial when evaluating AD therapeutics using the 5xFAD model.

Disclosures: J. Lee: None. **K. Park:** None. **S. Lee:** None. **Y. Kim:** None. **Y. Kang:** None. **A. Lee:** None. **T. Kim:** None. **S. Na:** None. **P.J. Sweeney:** None. **L. Park:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer’s Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.29/B99

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

Support: Forever Healthy Foundation
Larry L. Hillblom Foundation Fellowship

Title: A KIBRA-derived peptide rescues synaptic plasticity and memory loss in Tauopathy model

Authors: *L. YAO, I. WONG, G. KAUWE, K. PAREJA-NAVARRO, Y. NGWALA, T. E. TRACY;
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Abstract: Long-term potentiation (LTP) is a type of synaptic plasticity that is the cellular basis of learning and memory formation. LTP impairment in the hippocampus is commonly associated with memory deficits in mouse models of tauopathy including Alzheimer's disease. In a mouse model of pathological tau hyperacetylation found in tauopathy (tauKQ^{high} mice), we recently demonstrated that lentivirus-based overexpression of the C-terminal domain of KIBRA (CT-KIBRA) in hippocampus reverses both LTP impairment and memory deficits in the mice despite the accumulation of pathogenic tau in the brain. Thus, KIBRA-mediated synaptic repair is a potential therapeutic avenue for reversing memory loss in AD. To design a therapeutic strategy that could be translational for synapse repair, here, we engineered a cell-permeable KIBRA-derived peptide (KB_{pep}) to mimic the functional properties of CT-KIBRA. Using co-precipitation methods, we confirmed that KB_{pep} interacts with different PKC isoforms, including PKMζ, which is a key downstream target of CT-KIBRA. We used a chemical long-term potentiation (cLTP) induction method to study postsynaptic trafficking of GluA1-containing AMPA-type glutamate receptors (AMPARs) during LTP in cultured rat hippocampal neurons and in human induced pluripotent stem cell (iPSC)-derived neuron tauopathy models. In hippocampal neurons, pathogenic tau blocked GluA1-containing AMPAR insertion into postsynaptic spines during LTP, and KB_{pep} treatment restored the AMPAR delivery to the spine surface despite the expression of pathogenic tau. In human iPSC-derived neurons with the tauV337M mutation that causes frontotemporal dementia, cLTP-induced postsynaptic AMPAR insertion was blocked while KB_{pep} treatment reinstated AMPAR trafficking during LTP. To study the effects of KB_{pep} in vivo, KB_{pep} was continuously delivered to the lateral ventricle of tauKQ^{high} mice, which have impaired long-term potentiation (LTP) in dentate gyrus (DG) and hippocampal-dependent memory impairment. KB_{pep} treatment rescued LTP in DG and pattern separation and spatial memory in tauKQ^{high} mice. These findings support the therapeutic potential of KB_{pep} in reversing tauopathy-related synaptic plasticity impairment and memory loss.

Disclosures: L. Yao: None. **I. Wong:** None. **G. Kauwe:** None. **K. Pareja-Navarro:** None. **Y. Ngwala:** None. **T.E. Tracy:** None.

Poster

PSTR107: Mouse Model Strategies for Alzheimer's Disease I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.30/B100

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

Title: Exploring the antidepressant potential of Delonix regia extracts: Insights into mitigating depression and oxidative stress

Authors: *S. SINGH[1], S. SARDANA[2], I. VERMA[3];
[1]Pharm., Amity Inst. of Pharmacy, Amity University, Gurugram, Gurugram, India; [2]Pharm., Amity Inst. of Pharmacy, Amity Univ., Gurugram, India; [3]Pharm., MM Col. of Pharmacy, Maharishi Markandeshwar Deemed-to-be-University, Ambala, India

Abstract: Depression, a debilitating mental health condition affecting millions worldwide, presents a complex interplay of biological, psychological, and environmental factors. According to the World Health Organization (WHO), depression is a leading cause of disability globally, emphasizing the urgency for effective treatment strategies. While conventional pharmacotherapies such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and Monoamine Oxidase Inhibitors (MAOIs) are commonly prescribed, there is growing interest in exploring alternative or adjunctive therapies, including botanical remedies. In this study we investigated, the antidepressant potential of different extracts of *Delonix regia* dosed at 200, and 400 mg/kg. To induce anxiety and depression-like behaviors, Reserpine was administered intraperitoneally to the rat at a dose of 0.5 mg/kg in PBS containing 0.1% dimethylsulfoxide and 0.3% Tween-80) at a dose of 100 µL dose. The antidepressant activity was investigated by leveraging the Actophotometer test, Forced swimming test (FST), and Tail suspension test (TST) models. Fluoxetine, a benchmark pharmaceutical agent, served as a reference standard. Administration of different extracts of *Delonix regia* (at 200, 400 mg/kg) was found to have a significant ameliorating effect on depression and a moderating effect on oxidative and nitrosative stress. The findings suggest *Delonix regia* extracts (200, 400 mg/kg) can serve as a potential antidepressant both individually and as adjunctive agents in the treatment of depression. Inhibition of the inflammatory mediators during stress procedures or any other potential physiological and biochemical mechanisms may be involved in its antidepressant effect.

Disclosures: S. Singh: None. **S. Sardana:** None. **I. Verma:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.01/B101

Topic: C.06. Neuromuscular Diseases

Support: Laurence and Sandi Gluck Charitable Foundation

Title: Investigating disease mechanisms in sporadic ALS: Role of low-density lipoprotein receptor and sortilin in CSF-mediated motor neuron degeneration

Authors: *J. K. WONG, S. M. KOVALEV, G. L. CIACCIO, A. E. MCDERMOTT, S. A. SADIQ;
Tisch MS Res. Ctr. of NY, New York, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is characterized by progressive motor neuron degeneration which typically leads to death within 3 to 5 years following disease onset. We previously developed an animal model specific for sporadic ALS (sALS), the predominant subtype which accounts for 90% of ALS cases (Wong et al., 2022). Intrathecal delivery of cerebrospinal fluid (CSF) from sALS patients, but not familial ALS patients, induced motor disability and motor neuron degeneration in our mouse model. Furthermore, we identified apolipoprotein B-100 (ApoB) as the neurotoxic factor in sALS CSF responsible for inducing disease pathology. ApoB is known to bind to low-density lipoprotein receptors (LDLR) and sortilin. However, whether these ApoB receptors are critical for ApoB-induced cell death is unknown. Here, we aimed to identify which receptors mediate ApoB-induced motor neuron degeneration using *in vivo* and *in vitro* models of sALS. To assess ApoB-induced changes in LDLR and sortilin expression, adult female C57BL/6J mice underwent laminectomies at cervical levels 4 and 5, then received 3 µl injections into the subarachnoid space of: 1) saline, 2) sALS CSF, 3) ApoB-depleted sALS CSF, or 4) human ApoB protein. Forelimb motor deficits were assessed at 1 day post injection, then mice were perfused for ChAT, LDLR and sortilin immunostaining. The percentage of $ChAT^+$ motor neurons expressing LDLR or sortilin was quantified. All motor and histological assessments were performed blinded. To determine which receptors mediate ApoB-induced neurotoxicity, human iPSC-derived motor neurons (HMNs) were cultured for 8 days then treated for 24 hours with: 1) ApoB, 2) sortilin antibody + ApoB, or 3) LDLR antibody + ApoB. HMNs were fixed in 4% paraformaldehyde for ChAT, LDLR and sortilin immunocytochemistry. Mice injected with sALS CSF or ApoB developed significant forelimb motor disability and motor neuron loss compared to mice injected with saline or ApoB-depleted sALS CSF. This pathology correlated with upregulation of both LDLR and sortilin receptors on motor neurons. LDLR and sortilin were also significantly upregulated in ApoB-treated HMNs. ApoB-treated HMNs and sortilin antibody + ApoB-treated HMNs were significantly smaller than untreated HMNs, whereas HMNs treated with LDLR antibody + ApoB had similar cluster sizes as untreated HMNs, indicating that blocking LDLR prevents ApoB-induced cell death. Overall, our data suggest that LDLR, but not sortilin, plays a critical role in mediating ApoB-induced motor neuron death in sALS. We aim to elucidate signaling mechanisms downstream of LDLR that lead to motor neuron degeneration in future studies.

Disclosures: J.K. Wong: None. **S.M. Kovalev:** None. **G.L. Ciaccio:** None. **A.E. McDermott:** None. **S.A. Sadiq:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.02/B102

Topic: C.06. Neuromuscular Diseases

Title: A transgenic rat expressing the SOD1-G93A mutation exhibits ALS-like phenotypes, rendering it an effective translational model for drug development.

Authors: C. BIRD[1], L. HOOD[1], N. MEINERZ[1], H. ROBBINS[1], J. SHUSTERMAN[1], J. RAMADHIN[2], ***M. JACOBSON**[2], M. CARR[2], C. BUTT[1];
[1]Neuroscience, Inotiv, Inc., Boulder, CO; [2]Taconic Biosci., Rensselaer, NY

Abstract: Drug discovery for Amyotrophic Lateral Sclerosis (ALS) is crucial due to the absence of effective treatments for this debilitating neurodegenerative disease. ALS is characterized by the progressive degeneration of motor neurons, resulting in muscle weakness and eventual paralysis. Among the genetic factors in ALS, mutations in the gene for superoxide dismutase 1 (SOD1) have been associated with the familial form of the disease. As the encoded enzyme is critical for managing oxidative stress, mutated SOD1 has been linked to toxic effects on motor neurons. The SOD1 Rat (carrying a transgene for human SOD1 with the G93A mutation) was validated in a 16-week longitudinal study, and motor phenotypes correlated to a clinically relevant biomarker. In comparison to wild type controls, SOD1G93A rats exhibited progressive loss of motor coordination as measured in beam walk and rotarod assays, progressive degeneration of body condition, posture, locomotor activity and body weight as determined by clinical observations, and reduced survival over time. Mutants also expressed progressive increases in plasma neurofilament light, a measure of neuronal damage, and stable, significant levels of the mutated SOD1 enzyme in the plasma. Mutants also exhibited a notable loss of choline acetyltransferase immunoreactivity in the lumbar spinal cord, strongly suggesting an associated loss of cholinergic motor neurons. These findings underscore the relevance of the SOD1G93A rat to major aspects of ALS, making it an invaluable tool in the development of potential therapeutics for the disease.

Disclosures: C. Bird: A. Employment/Salary (full or part-time):; Inotiv, Inc. **L. Hood:** A. Employment/Salary (full or part-time):; Inotiv, Inc. **N. Meinerz:** A. Employment/Salary (full or part-time):; Inotiv, Inc. **H. Robbins:** A. Employment/Salary (full or part-time):; Inotiv, Inc. **J. Shusterman:** A. Employment/Salary (full or part-time):; Inotiv, Inc. **J. Ramadhin:** A. Employment/Salary (full or part-time):; Taconic Biosciences, Inc. **M. Jacobson:** A. Employment/Salary (full or part-time):; Taconic Biosciences, Inc. **M. Carr:** A. Employment/Salary (full or part-time):; Taconic Biosciences, Inc. **C. Butt:** A. Employment/Salary (full or part-time):; Inotiv, Inc..

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.03/B103

Topic: C.06. Neuromuscular Diseases

Title: Characterization of a SOD1 Rat Model of ALS: Behavior and Electrophysiology

Authors: A. ZAJICEK[1], B. HANER[1], M. OSBORNE[1], M. L. JACOBSON[2], M. CARR[2], ***T. HANANIA**[1];
[1]PsychoGenics, Inc., Paramus, NJ; [2]Taconic Biosci., Inc., Rensselaer, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder characterized by progressive motor neuron degeneration resulting in muscle weakness, paralysis, and eventually death. Mutations of the superoxide dismutase 1 (SOD1) gene are linked to familial and sporadic cases of ALS. In collaboration with Taconic Biosciences, PsychoGenics characterized a SOD1 G93A overexpressing rat [Ntac:SD-Tg(SOD1G93A)L26H] model of ALS. Male and female wild type (WT) and transgenic (Tg) rats were used in the study. Fifteen rats were enrolled in each group which allowed us to assess phenotypic differences in male and female rats. Body weight (BW), motor function, and nerve conduction changes were measured longitudinally starting at 16 weeks of age. SOD1 rats showed progressive decrease in BW. Deficits in hindlimb grip strength started at 24 weeks of age, whereas decreased locomotor and rearing activities occurred at 29 weeks of age. Deficits in rotarod performance were also seen in the SOD1 rats starting at 22 weeks of age. In general, the behavioral deficits were more robust in male SOD1 rats compared to female rats. Survival analysis showed that female rats survived longer than male rats. Assessment of compound muscle action potential (CMAP) found that starting at 24 weeks of age, onset latency, which corresponds to the time from initiation of nerve stimulus to response, was increased in SOD1 rats. Peak amplitude and neuromuscular conduction velocity were reduced in SOD1 rats compared to WT rats. Additional marker analysis are ongoing. Together, these results suggest that this model can be used for screening novel therapeutics for ALS treatment.

Disclosures: A. Zajicek: A. Employment/Salary (full or part-time):; PsychoGenics, Inc. **B. Haner:** A. Employment/Salary (full or part-time):; PsychoGenics, Inc. **M. Osborne:** A. Employment/Salary (full or part-time):; PsychoGenics, Inc. **M.L. Jacobson:** A. Employment/Salary (full or part-time):; Taconic Biosciences, Inc. **M. Carr:** A. Employment/Salary (full or part-time):; Taconic Biosciences, Inc. **T. Hanania:** A. Employment/Salary (full or part-time):; PsychoGenics, Inc.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.04/B104

Topic: C.06. Neuromuscular Diseases

Title: Novel Changes to Perineuronal Nets in Amyotrophic Lateral Sclerosis Mouse Model

Authors: J. PINEDA[1,3], I. ALLODI[4], *M. T. TONG[2];
[1]Neurosci., Macalester Col., St Paul, MN; [2]Biol., Macalester Col., Saint Paul, MN; [3]Stanley Ctr. for Psychiatric Res., The Broad Inst. of MIT and Harvard, Cambridge, MA; [4]Univ. of St Andrews, Sch. of Psychology and Neurosci., St Andrews, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the progressive loss of motor function through the degeneration of motor neurons in the spinal cord. Previous research has indicated a pivotal role of glycinergic V1 inhibitory interneurons in modulating both motor neuron activity and locomotion (Allodi 2021). The canonical loss of motor neurons in ALS is due to the loss of synaptic connections from the early loss of these Gly+ interneurons (Allodi 2021; Mora 2022). Perineuronal nets (PNNs), primarily composed of chondroitin sulfate proteoglycans, are known for their involvement in synapse stabilization and have been proposed to offer neuroprotective effects elsewhere in the nervous system. In this study, we look at PNN expression throughout pre-symptomatic (P45, P60, P84) and symptomatic (P112) stages of ALS disease in male and female SOD-1-GlyT2GFP mice, a recognized ALS model. We used immunohistochemistry to investigate PNN number and distribution within the cervical spinal cord, specifically their co-localization with glycinergic interneurons and motor neurons. Analyses using two-way ANOVAs (genotype: wild-type or SOD-1 by age: P45, P60, P84, P112) revealed a significant interaction between age and genotype for the number of motor neurons, number of PNNs, and number of Gly+ interneurons. Post-hoc tests confirmed both motor neuron and Gly+ interneuron loss with age in the SOD-1 mouse. Interestingly, we found that while wild-type mice showed an increase in the proportion of Gly+ interneurons surrounded by PNNs with age, the SOD-1 mice showed a decrease. We also observed PNNs in the dorsal horn of the spinal cord, a known sensory input region, around gly- cells. The number of PNNs in this region also decreased with age in the SOD-1, but not wild-type mice. Taken together, our novel findings suggest a significant role of PNNs in ALS-associated neuron loss and offer a critical new avenue for exploration.

Disclosures: J. Pineda: None. **I. Allodi:** None. **M.T. Tong:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.05/B105

Topic: C.06. Neuromuscular Diseases

Support: NINDS R21NS120126 (to GM)
Neurodegenerative Research Inc. (to GM)

Title: Addressing contributions of aberrant p38alpha MAPK signaling to axonal degeneration in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis

Authors: *L. NORIEGA[1], M. PRIEGO LUQUE[1], V. OCCHIEPPO[1], P. BOTTU[1], M. GANZORIG[1], A. YALAVARTHI[1], H. ZAKY[1], U. BHATTACHARYYA[1], H. MARCHADI[1], T. A. HATZIPETROS[2], G. A. MORFINI[1];
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Abstract: Axonal pathology represents an early pathogenic event affecting motor neurons in both familiar and sporadic forms of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disorder. The mechanism(s) by which axons degenerate in ALS are largely unknown. Numerous independent studies documented alterations in fast axonal transport (FAT), a major cellular process sustaining axonal heath, in a wide variety of familial ALS (fALS) models, including transgenic mice expressing mutant forms of superoxide dismutase 1 (mSOD1). The potential disease relevance of these observations was highlighted by genetic evidence showing that mutations in motor proteins powering FAT *suffice* to cause axonopathy and degeneration of motor neurons, but a mechanistic basis linking mSOD1 to such deficits remained elusive. Filling this gap in our knowledge, our studies in isolated squid axons showed that the toxic effect of mSOD1 proteins on FAT involves abnormal activation of the protein kinase p38alpha (p38α) and aberrant phosphorylation of axonal proteins, including the motor protein kinesin-1 and neurofilaments.Although numerous reports spanning decades documented enhanced phosphorylation (and hence activation) of p38 kinases, in ALS-affected tissues and mSOD1-based fALS mouse models, their potential contribution to axonal pathology elicited by mutant SOD1 *in vivo* remained unknown. We addressed this gap in our knowledge by examining specific contributions of p38α, the most abundant p38 isoform expressed in neurons. Towards this, we used a genetic approach to promote ubiquitous attenuation of p38α signaling in transgenic $SOD1^{G93A}$ mice, an animal model where the axonal pathology phenotype of ALS is faithfully recapitulated. Remarkably, we found that genetically-based attenuation of p38α signaling in $SOD1^{G93A}$ mice prevented degeneration of spinal cord axons and loss of spinal motor neurons at an age when motor deficits are already manifested in this model. Interestingly, this effect was not associated with changes in transgenic mSOD1 expression and glial activation. Collectively, our findings reveal a significant contribution of p38-alpha to mutant SOD1-induced axonal pathology and neuronal preservation, suggesting this kinase might represent a potential therapeutic target to treat ALS.

Disclosures: L. Noriega: None. **M. Priego Luque:** None. **V. Occhieppo:** None. **P. Bottu:** None. **M. Ganzorig:** None. **A. Yalavarthi:** None. **H. Zaky:** None. **U. Bhattacharyya:** None. **H. Marchadi:** None. **T.A. Hatzipetros:** None. **G.A. Morfini:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.06/B106

Topic: C.06. Neuromuscular Diseases

Title: Early synaptic and gait changes in the SOD1 G93A mouse model of ALS

Authors: *J. TOIVANEN[1,2], J. ROKKA[1], T. BRAGGE[1], P. POUTIAINEN[3], J. RYTKÖNEN[1], S. BÄCK[1];
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Abstract: Recently, changes in synaptic density have been recognized as an early occurrence in ALS patients preceding motor neuron death and neuromuscular junction disintegration. Here we used the SOD1-G93A mouse model to assess changes in synaptic density and gait before the emergence of observable weakness and at the early symptomatic phase. For this purpose, 12 female $SOD1^{G93A}$ transgenic (TG) mice (JAX stock: 002726) and 12 wild-type littermate controls were subjected to kinematic gait analysis and SV2A-targeting P[18F]SynVesT1-PET imaging at 6, 8, 10 and 12 weeks of age. In addition, traditional motor phenotype assessment by rotarod was performed at 6, 8 and 10 weeks for comparison. The mice were dosed with 5-10 MBq activity and in vivo PET imaging was performed with small animal PET/CT (NanoPET, BioScan). Kinematic gait analysis was performed by capturing ventral, left and right view high-speed videos using the Motorater® system (TSE systems). Principal component analysis (PCA) was used to create a disease model fingerprint and overall gait score at each time point for both groups. Based on a preliminary analysis on the PET data, the most notable finding was a trending effect of 5.9% decrease in P[18F]SynVesT1 binding in the whole cerebral cortex at 12 weeks in SOD^{G93A} mice (p=0.225926). $SOD1^{G93A}$ mice exhibited a significantly different overall gait score already at 6 weeks with gradual progression at each time point until 12 weeks whereas rotarod performance was compromised from 8 weeks only. Overall, the $SOD1^{G93A}$ mice walked slower than the WT mice from 8 weeks onwards. Consistent differences over time were lower tail base and tip height and altered limb trajectory profiles. In conclusion, kinematic gait analysis can be used to assess the effects of preclinical therapeutic interventions in $SOD1^{G93A}$ mice in the very early phase. PET data analysis will be continued by delineating the motor cortex and other cortical areas and by assessing the time course data to confirm the preliminary finding of lowered synaptic density.

Disclosures: J. Toivanen: A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **J. Rokka:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **T. Bragge:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **P. Poutiainen:** None. **J. Rytkönen:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **S. Bäck:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.07/B107

Topic: C.06. Neuromuscular Diseases

Support: ●Startup funds from the College of Pharmacy, the Provost Office and The George and Anne Ryan Institute for Neuroscience
●NIH NINDS R01 NS110953

Title: Dysregulation of homeostatic plasticity in ALS: investigating the homeostatic response of mutant SOD1 mouse spinal motoneurons to chronic diazepam treatment

Authors: E. REEDICH, R. MANUEL, *M. MANUEL;
Dept. of Biomed. and Pharmaceut. Sci., Col. of Pharm., Univ. of Rhode Island, Kingston, RI

Abstract: Dysregulation of homeostatic plasticity has recently emerged as a potential overarching mechanism underlying motoneuron disease pathophysiology. In this context, we are investigating the dysregulation of homeostatic plasticity using mutant SOD1 mice as a model system for neurodegenerative motoneuron diseases. We propose that mutant SOD1 motoneurons exhibit dysregulated homeostatic plasticity, characterized by overcompensation and subsequent oscillations, resulting in increased motoneuron morbidity.
We are rigorously testing this hypothesis by investigating the homeostatic response of mutant SOD1 motoneurons to chronic diazepam treatment, a benzodiazepine that exerts its effects through enhancing the inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) receptors.
This double-blind study includes four experimental groups: SOD1-G93A mice treated with diazepam, SOD1-G93A mice treated with vehicle only, wild-type (wt) littermates treated with diazepam, and wt littermates treated with vehicle only. Mice are treated with daily injections of diazepam (15 mg/kg, SC) or the vehicle alone for 10 days, with the last treatment administered on the day of the recording.
Intracellular recordings of motoneurons are performed at age 45-55 days old, encompassing a critical period of disease progression. We are assessing changes in intrinsic excitability and firing properties of motoneurons, including measurements of input resistance, rheobase, and firing rates. Furthermore, synaptic inputs, both excitatory and inhibitory, are investigated to evaluate alterations in the balance of synaptic transmission.
Based on the hypothesis of dysregulation of homeostatic plasticity, we predict that mutant SOD1 motoneurons will exhibit exaggerated homeostatic responses following chronic diazepam treatment compared to wt littermates. Specifically, we expect that the chronic treatment will lead to alterations in the intrinsic electrical properties, resulting in increased firing rates and enhanced excitatory synaptic transmission, in both mutant SOD1 and wt control motoneurons, but that these alterations will be more pronounced in the mutant group.
Our preliminary results suggest that chronic diazepam treatment induces homeostatic plasticity in wt and mutant SOD1 motoneurons. There seems to be an interaction between treatment and genotype, with mutant SOD1 motoneurons responding differently to the homeostatic challenge of chronic diazepam treatment. The difference in responses to the diazepam treatment between mutant SOD1 and wt motoneurons suggests a dysregulated homeostatic gain in mutant SOD1 motoneurons.

Disclosures: E. Reedich: None. **R. Manuel:** None. **M. Manuel:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.08/B108

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH grant T32 HD07418
Les Turner ALS Foundation

Title: Ambient glutamate and motoneuronal excitability: the role of system x_c^- in ALS pathogenesis

Authors: *B. S. HEIT, M. JIANG, C. J. HECKMAN;
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Abstract: Glutamate excitotoxicity is an important mediator in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS). In both human and animal studies, neural networks exhibit elevated extracellular glutamate concentrations coupled with hyperexcitability which ultimately beget denervation. Not surprisingly, the contribution of *synaptic* glutamate has been heavily scrutinized in ALS etiology; the role of ambient, *extrasynaptic* glutamate, however, has yet to be examined in this regard. In the CNS, ambient glutamate is regulated by the cystine/glutamate antiporter, system x_c^-, with protein subunit xCT. Importantly, the antiporter is markedly upregulated in both animal ALS models and human patients. Remarkably, transgenic mice lacking a functional system x_c^- ($xCT^{-/-}$ mice) exhibit extended lifespan as well as 60-80% lower ambient glutamate concentrations when compared to wild-type (WT) controls. In contrast, $SOD1^{G93A}$ mice, a transgenic model for ALS pathology, display truncated lifespan, enhanced system x_c^- activity, and elevated ambient glutamate concentrations. In the current study, we explored the role of ambient glutamate in ALS by assessing the antiporter's contribution to the deleterious hyperexcitability of motoneurons. We employed a novel *in vitro* spinal cord preparation to electrophysiologically measure motoneuronal excitability in $xCT^{-/-}$, WT, and $SOD1^{G93A}$ mice. Additionally, cerebral spinal fluid (CSF) was sampled from each genotype, and glutamate concentrations were analyzed using mass spectrometry. Our results revealed decreased motoneuronal excitability in $xCT^{-/-}$ mice, as evidenced by enhanced short-term depression (STD), when compared to WT and $SOD1^{G93A}$ counterparts. Contrarily, $SOD1^{G93A}$ mice exhibited attenuated STD as compared to $xCT^{-/-}$ and WT mice, thus revealing increased motoneuronal excitability. Furthermore, the decreased excitability in $xCT^{-/-}$ mice was concomitant to reduced CSF glutamate levels, whereas the increased excitability in $SOD1^{G93A}$ mice was attendant to elevated glutamate levels. These data suggest that ALS-induced system x_c^- upregulation, and the obligate release of ambient glutamate, heighten presynaptic calcium loading and drive the motoneuronal hyperexcitability which leads to degeneration. Ongoing experimentation will i) confirm whether pharmacological antagonism of system x_c^- can mitigate hyperexcitability and ii) probe the mechanism by which ambient glutamate alters synaptic properties in the disease. Collectively, our data portend a novel therapeutic intervention which may ameliorate glutamate excitotoxicity in ALS thereby attenuating or precluding motoneuronal dysfunction.

Disclosures: B.S. Heit: None. **M. Jiang:** None. **C.J. Heckman:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.09/B109

Topic: C.06. Neuromuscular Diseases

Title: Cholinergic antagonists improve behavioural performance, muscle innervation at end stage, and life expectancy in ALS animal model.

Authors: *R. POPOLI[1], T. L. WELLS[1], T. AKAY[2];
[1]Med. Neurosci., Dalhousie Univ., Halifax, NS, Canada; [2]Dept. of Med. Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: In ALS, symptom onset does not occur until a significant number of motor neurons have died, suggesting the existence of a compensatory mechanism. Our previous research has shown that genetically silencing C-boutons in ALS mutant mSOD1^{G93A} mice leads to earlier symptom onset and worsening of behavioural performance. This suggests that these synapses are involved in a delayed symptom onset relative to motor neuron death. We have previously shown that C-boutons are upregulated during intensive exercise routines, such as swimming. Moreover, the literature suggests that this type of exercise is detrimental to disease progression in mSOD1^{G93A} mice. However, when the C-boutons are genetically silenced and mice are exercised three times a week in the form of swimming, an activity where these synapses would typically be upregulated, behavioural performance is dramatically improved. Genetic manipulations, however, are not used in clinical settings, presenting a challenge to improving neurological care in patients with ALS. In our most recent study, we investigated a clinically relevant approach through the use of two cholinergic antagonists in two conditions: (i) frequent exercise under the influence of these pharmacological agents and (ii) resting conditions. These groups were compared among themselves, along with saline controls. Statistical analyses were performed with sample sizes sufficiently large to provide a statistical power of at least 80%. Our results show that both pharmacological agents improve behavioural performance and increase lifespan by approximately 8%, suggesting it may improve the quality of life in patients with ALS. Histological analyses also show that one of these cholinergic antagonists significantly improves muscle innervation at end-stage compared with controls. Based on these results, however, it is unclear whether these positive effects are C-bouton dependent or not since these drugs act on several cholinergic systems in the body. In order to reveal whether the mechanism behind these positive results is C-bouton dependent, we repeated the previous experiments in mice with genetically silenced C-boutons (mSOD1^{G93A} ; Dbx1::cre; ChAT$^{fl/fl}$;mSOD1^{G93A} /C^{off}). Our preliminary results suggest that behavioural performance does not seem to be affected by the cholinergic antagonist in the absence of functional C-boutons. However, weight, lifespan, and muscle innervation at end-stage seem to improve in the treatment group compared to controls. These results suggest that the beneficial effects of the cholinergic antagonists are not solely C-bouton dependent and may be due to a combination of both central and peripheral effects.

Disclosures: R. Popoli: None. **T.L. Wells:** None. **T. Akay:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.10/B110

Topic: C.06. Neuromuscular Diseases

Support: National Natural Science Foundation of China

Title: Specific effects of cytoplasmic TDP-43 in the non-human primate models

Authors: *Q. JIA[1,2], Z. LONGHONG[1,2], X.-J. LI[1,2], P. YIN[1,2];
[1]Jinan Univ., Guangzhou, China; [2]Guangdong Key Laboratory of Non-human Primate Research, Guangdong-Hongkong-Macau Institute of CNS Regeneration, Guangzhou, China

Abstract: The cytoplasmic accumulation of TAR DNA-binding protein 43 (TDP-43) is a significant pathological feature observed in various conditions such as amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), and Parkinson's disease (PD). However, in most mouse models expressing mutant TDP-43, there is a predominant distribution of mutant TDP-43 in the nucleus, which limits the exploration of the cytoplasmic effects of mutant TDP-43. By inducing the expression of mutant TDP-43 in both monkey and mouse brains, we have uncovered that the primate-specific caspase-4 cleaves TDP-43, generating fragments capable of translocating from the nucleus to the cytoplasm. This process is implicated in the mislocalization of TDP-43 within patient brains. Subsequent investigations into the primate-specific impacts of cytoplasmic TDP-43 in monkeys have revealed its influence on reducing SQSTM1 mRNA stability, whereas the loss of nuclear TDP-43 suppresses *PJA1* gene transcription in monkeys but not in mouse brains. These discoveries offer valuable insights into TDP-43 mediated pathology by examining cytoplasmic TDP-43. Additionally, we have developed a transgenic mouse model expressing the human *caspase-4* gene and observed that these mice can replicate the cytoplasmic mislocalization of endogenous TDP-43 and motor dysfunction in an age-dependent manner, rendering them a valuable and innovative mouse model for further investigations into the pathogenesis mediated by endogenous TDP-43.

Disclosures: Q. Jia: None. **Z. longhong:** None. **X. Li:** None. **P. Yin:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.11/B111

Topic: C.06. Neuromuscular Diseases

Support: Neurological Fund Denmark

Title: The axonal effects of TDP-43 pathology in TDP-43 (ΔNLS) mice.

Authors: *V. REHAKOVA[1,2], C. F. MEEHAN[2];
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Abstract: Nerve excitability tests have consistently revealed an increased excitability of peripheral motoneurone axons in individuals with ALS, consistent with the increased presence of fasciculations. Such studies indicate an imbalance between axonal potassium and sodium currents in this disease, although what is driving these changes at the cellular level is unclear. In the G93A SOD1 mouse model of ALS, we have previously shown similar excitability changes correlating with structural alterations in nodes of Ranvier (NoR). This included decreases in nodal diameter, increases in nodal length and a loss of paranodal/juxta-paranodal integrity. However, SOD1 mutations account for only ~2% of all ALS and lack cytoplasmic TDP-43 inclusions - the hallmark pathological feature seen in more than 97% of ALS cases. Thus, the cause behind the excitability changes in peripheral axons for the vast majority of patients remains unknown.
The TDP-43(ΔNLS) mouse model recapitulates the TDP-43 pathology seen in ALS using a Tet-on/off expression system, allowing for inducible expression of cytoplasmic TDP-43 aggregates. Using this mouse, we have previously demonstrated that TDP-43 pathology is sufficient to drive increased excitability centrally in spinal motoneurones, partly via changes in axonal initial segment geometry. We therefore hypothesized that TDP-43 pathology may also drive structural changes more distally in nodes of Ranvier that may explain the peripheral hyper-excitability in this disease. Immunohistochemistry was used to label Nav channels (restricted to nodes), Caspr-1 (restricted to paranodes) and Kv1.2 channels (restricted to juxtaparanodes) in TDP-43(ΔNLS) of both sexes at 2.5 weeks post-transgene induction and compared these to tetracycline activator only controls as well as in mice in which the transgene had been expressed for 4 weeks and then re-suppressed for ~6 weeks. Nodal regions exhibited a significant reduction in diameter in induced TDP-43(ΔNLS) mice, a change that was only partially reversed following transgene re-suppression. Increased paranodal length was also observed, along with pronounced disruptions in the localization of Caspr-1 and Kv1.2 at paranodal-juxtaparanodal regions. These disruptions were reduced by transgene re-suppression.
Conclusion: TDP-43 pathology is sufficient to drive structural changes in NoR, which are only partly reversible. Thus, we propose that TDP-43 pathology may be driving the peripheral hyper-excitability seen in this disease.

Disclosures: V. Rehakova: A. Employment/Salary (full or part-time):; 2N Pharma. **C.F. Meehan:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.12/B112

Topic: C.06. Neuromuscular Diseases

Title: Phenotyping of the rNLS8 model of TDP-43 pathology to support ALS drug discovery

Authors: J. TOIVANEN, Y. SINGH, L. RAUHALA, T.-K. STENIUS, *K. LEHTIMÄKI, S. BÄCK;
Charles River Discovery Res. Services, Kuopio, Finland

Abstract: TAR DNA Binding Protein 34 kDa (TDP-43) pathology is linked to familial and sporadic forms of amyotrophic lateral sclerosis (ALS). Cytoplasmic aggregates containing TDP-43 are observed in almost all ALS cases and mutations in TDP-43 are causative for disease. TDP-43 pathology is therefore central to understand the disease and has become an important focus for drug discovery efforts.
To support future in vivo pharmacology and efficacy studies, our aim was to phenotype the rNLS8 mouse line, verifying the behavioral and biomarker finding previously described in literature (Walker et al. Acta Neuropathol 130, 2015). The rNLS8 model is a double transgenic model characterized by doxycycline (Dox)-suppressible expression of human TDP-43 with a defective nuclear localization signal.
All animal work was conducted in accordance with European Union directive 2010/63 and approved by the national Project Authorisation Board. A total of n=11 male and female rNLS8 (B6;C3-Tg(NEFH-tTA)8Vle Tg(tetO-TARDBP*)4Vle/J, The Jackson Laboratory, ID 028412) double transgenic mice were used. The control group consisted of n=7 tTA mice lacking the tetO-hTDP-43-ΔNLS transgene. The in-life phenotype prior to and after Dox removal was assessed using clinical scores, body weights, limb strength, wire hang and rotarod. Ex vivo biomarker assessment at 4 weeks after Dox removal included anterior horn motor neuron counts and TDP-43 expression in the lumbar spinal cord, analysis of neuromuscular junction (NMJ) integrity of the gastrocnemius muscle, and measurements of cerebrospinal fluid (CSF) levels of neurofilament light chain (NfL).
The rNLS8 mice showed significant impairment in the rotarod and wire hang performance and a progressive decline in body weight and observable limb weakness. Ex vivo analyses revealed increased total and phosphorylated TDP-43 expression and a decrease in the nuclear to cytoplasmic ratio of TDP-43 as compared to the tTA control mice. Motor endplate pathology was observed as an increase in denervated NMJs and elevated CSF NfL levels suggested extensive axonal damage. No significant loss of motor neurons was observed 4 weeks after Dox removal. Our results are in line with published literature and show that the rNLS8 mouse model manifests an ALS-like in vivo phenotype accompanied by motor neuron TPD-43-pathology and NMJ disintegration. Together with novel in vitro models, such as CRISPR-edited induced pluripotent stem cells (iPSC), animal models of TDP-43 pathology will serve as important tools to enhance ALS drug discovery.

Disclosures: J. Toivanen: A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **Y. Singh:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **L. Rauhala:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **T. Stenius:** A. Employment/Salary (full or part-time):;

Charles River Discovery Research Services. **K. Lehtimäki:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **S. Bäck:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.13/B113

Topic: B.09. Glial Mechanisms

Support: RF1AG082314
R35NS132326

Title: Microglial Regulation of Motor Cortical Excitability in TDP-43 related neurodegeneration

Authors: *M. XIE[1], L.-J. WU[2];
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Abstract: Motor cortical hyperexcitability is a phenomenon well-documented in the presymptomatic stage of amyotrophic lateral sclerosis (ALS). However, the mechanisms underlying and regulating this early dysfunction are not fully understood. Microglia, as the principal immune cells of the central nervous system, have emerged as important players in monitoring and modulating neuronal activity under both physiological and pathological conditions. In this study, we investigated the potential involvement of microglia in sensing and regulating neuronal activity and shaping the function of motor cortical circuits in an ALS mouse model (rNLS8). In this model, human TDP-43 without a nuclear localization sequence is expressed in a Dox-dependent manner. Upon initiating TDP-43 expression by removing the DOX diet, the mice exhibited characteristic motor deficits. This unique feature allowed us to precisely record neuronal activity during baseline and disease progression from the same animal. Utilizing multichannel probe recording and longitudinal *in vivo* calcium imaging in awake mice, we observed neuronal hyperactivity at the initial stage of disease progression. Spatial and single-cell RNA transcriptomics revealed microglia are the primary responders to motor cortical hyperactivity. Further examination identified a novel subpopulation of microglia which predominantly interact with dendrites, regulating motor cortical hyperactivity by attenuating excitatory synaptic input. Notably, the elimination of this microglia subpopulation through TREM2 knockout exacerbated motor deficits and further decreased survival rates. Overall, our results suggest that microglia may play a neuroprotective role by modulating motor cortical excitability in the rNLS8 mouse model.

Disclosures: M. Xie: None. **L. Wu:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.14/B114

Topic: C.06. Neuromuscular Diseases

Title: Cgas inhibition delays als progression in animal models

Authors: *Y. LIU[1], W. QU[2], S. C. SINHA[4], L. GAN[3];
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Abstract: Pathologic mislocalization of TAR-DNA binding protein 43kDa (TDP-43) induces neuroinflammatory response in amyotrophic lateral sclerosis (ALS), in which the activation of cyclic GMP-AMP (cGAMP) synthase (cGAS) and stimulator of interferon gene (STING) has been implicated. To assess if activation of cGAS plays a detrimental role in ALS-related disease progression, we treated two independent lines of TDP43 transgenic ALS mouse models with TDI-6570, a potent brain permeable cGAS inhibitor. In either TDP-43^{Q331K} mice expressing human TDP-43 protein with the ALS-associated Q331K, or TDP-43^{A315T} expressing ALS-associated A315T mutation, TDI treatment alleviated the pathological TDP-43 induced motor deficits on the rotarod or hindlimb test. Furthermore, TDI treatment ameliorated the metabolic abnormality of TDP-43^{Q331K} mice by increasing their food intake and decreasing their energy expenditure. At the cellular level, we found that the cGAS inhibition alleviated the phosphorylation of TDP-43 and improved the density of $NEUN^{+}$ cells in the cortex of TDP-43^{Q331K} mice. Single cell nucleus sequencing of these mice is underway to unravel the protective effect of cGAS inhibition at the transcriptomic. Interestingly, preliminary analyses revealed that the *CGAS* expression was downregulated in the postmortem spinal cord of ALS patients, particularly those with the hexanucleotide repeat expansion of *C9orf72*. Taken together, these data demonstrated that cGAS inhibition has a beneficial role in protecting the brain from pathological TDP-43 and showcase the feasibility of potentially using cGAS inhibitors to treat ALS.

Disclosures: Y. Liu: None. **W. Qu:** None. **S.C. Sinha:** Other; Subhash C. Sinha is a consultant of Aeton Therapeutics, Inc., and holds equity. **L. Gan:** Other; Li Gan is a founder and consultant of Aeton Therapeutics, Inc., and holds equity.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.15/B115

Topic: C.06. Neuromuscular Diseases

Support: PID2021-128906OB-I00
RTI2018-098885-B-I00
CB06/05/0089
PID2022-138461OB-I00

Title: Unraveling neuroprotective pathways: targeting enzymes that inactivate endocannabinoids for ALS therapeutic management

Authors: M. GÓMEZ-ALMERÍA[1,2,3], R. MARTIN BAQUERO[1,2,3], C. RODRÍGUEZ-CUETO[1,2,3], J. ROMERO[4], B. F. CRAVATT[5], U. GRETHER[6], J. FERNANDEZ-RUIZ[1,2,3], ***E. DE LAGO**[1,2,3];
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Abstract: The endocannabinoid system is involved in the pathophysiology of neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), so targeting some of its components has emerged as a promising therapeutic option. Specifically, an endocannabinoid-based therapeutic approach currently in progress in ALS is the inhibition of the inactivation of endocannabinoids by fatty acid hydrolase (FAAH) and monoacylglycerol lipase (MAGL) enzymes. This option holds considerable advantages compared to direct receptor activation, which may entail more pronounced side effects. Previous studies showed that genetic deletion of the FAAH enzyme and the pharmacological inhibition of MAGL slowed disease progression in the classic SOD-1 transgenic mouse model, which suggests that the elevation of endocannabinoid levels may provide an intrinsic protective action during the disease onset. We are now interested in investigating the benefits of modulating FAAH or MAGL enzymes in an alternative murine model of ALS as PrP-TDP43^{A315T} mice. We have employed three experimental strategies using these TDP43^{A315T} mice: (i) to induce genetic ablation of FAAH enzyme in these mice by their crossing with FAAH-deficient mice; (ii) to inhibit FAAH enzyme with the selective FAAH inhibitor URB597 (0.2 mg/kg) given i.p. from presymptomatic (PND65) to symptomatic stages (PND95); and (iii) to inhibit MAGL enzyme using the irreversible inhibitor RO727 (3 mg/kg) or the reversible inhibitor RO723 (10 mg/kg). The progression of the pathological phenotype in the three cases was recorded weekly using behavioral tests (rotarod and clasping tests), whereas their spinal cords obtained after sacrifice at the end of treatment were used to assess neuronal survival and glial reactivity. TDP43^{A315T}/FAAH$^{-/-}$ mice showed a delay in motor decline and increased survival compared with TDP-43^{A315T}/FAAH$^{+/+}$ mice. These improvements were associated with a higher preservation of spinal motor neurons and a significant decrease in Iba-1 immunoreactivity. The chronic treatment with URB597, RO723, or RO727 also reduced neuronal death in the spinal cord and, in some cases, also attenuated glial reactivity, although these benefits did not result in an improvement in behavioral responses. In summary, our results strongly suggest the neuroprotective potential of modulating endocannabinoid inactivation in ALS using genetic or pharmacological tools. This inactivation increased neuronal survival and attenuated glial reactivity, providing a promising avenue for further development toward the clinical scenario with pharmacological agents inhibiting FAAH and/or MAGL enzymes.

Disclosures: M. Gómez-Almería: None. **R. Martin Baquero:** None. **C. Rodríguez-Cueto:** None. **J. Romero:** None. **B.F. Cravatt:** None. **U. Grether:** None. **J. Fernandez-Ruiz:** None. **E. de Lago:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.16/B116

Topic: C.06. Neuromuscular Diseases

Support: UKDRI Animal Models Programme

Title: In-depth longitudinal behavioural, cognitive and sensory phenotyping of the new C9orf72GR400/+, and the TardbpQ331K/Q331K mouse model of ALS/FTD

Authors: *S. BOYANOVA[1,2], G. BANKS[3], R. S. BAINS[3], M. E. STEWART[3], S. WELLS[3], F. K. WISEMAN[2];
[1]UCL, London, United Kingdom; [2]UKDRI, Inst. of Neurol., Univ. Col. London, London, United Kingdom; [3]Mary Lyon Ctr. at MRC Harwell, Oxfordshire, Didcot, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), are adult-onset neurodegenerative diseases with overlapping clinical, pathological, and genetic origins. A GGGGCC (G4C2) hexanucleotide repeat expansion in the first intron of the C9ORF72 gene is the most common genetic cause of ALS and FTD. One potential disease mechanism and a major pathogenic feature of ALS/FTD, is expression of aberrant dipeptide repeat (DPR) proteins encoded in six frames by the hexanucleotide repeat. In addition, nearly all cases of ALS and approximately half of FTD cases, are characterised by cytoplasmic mislocalisation and aggregation of the TAR DNA-binding protein (TDP-43), encoded by the TARDBP gene. Over 50 TARDBP mutations have been identified in ALS/FTD. One such mutation is the n.991C>A (p.Q331K), producing a toxic TDP-43Q331K species. In order to understand the role of DPRs in vivo, a novel physiological C9orf72 DPR knock-in mouse model (C9orf72GR400/+) was created using CRISPR/Cas9 (Milioto et al., 2024). Here, we characterise this model alongside an established knock-in model of TDP-43 pathology (TardbpQ331K/Q331K) in a longitudinal cognitive and sensory behavioural study.
The mice underwent standardised pipeline of longitudinal behavioural testing at two timepoints 15-20, and 68-73 weeks of age. All experiments were completed in accordance with the ARRIVE 2.0 guidelines at the Mary Lyon Centre at MRC Harwell, UK.
We will present results from the three-chamber test of social motivation, the Sanderson forced alteration Y-maze test of short-term spatial memory, elevated plus maze test of anxiety-like behaviour, and the marble burying test. We have tested olfaction using the odour habituation-dishabituation test, and visual function using the optokinetic drum test, to understand if sensory confounds affect test performance. Weight, and echo-MRI data (from the TardbpQ331K/Q331K mice) will also be presented.

Using physiological mouse models and standardised phenotyping protocols is vital to ensure the reproducibility and translational value of studies using animal models, to understand the mechanisms underlying neurodegenerative diseases such as ALS/FTD and test the efficacy of new therapies.
Milioto, C., Carcolé, M., Giblin, A. et al. PolyGR and polyPR knock-in mice reveal a conserved neuroprotective extracellular matrix signature in C9orf72 ALS/FTD neurons. Nat Neurosci 27, 643-655 (2024). https://doi.org/10.1038/s41593-024-01589-4

Disclosures: S. Boyanova: None. **G. Banks:** None. **R.S. Bains:** None. **M.E. Stewart:** None. **S. Wells:** None. **F.K. Wiseman:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.17/B117

Topic: C.06. Neuromuscular Diseases

Support: Lundbeck Foundation Ascending Investigator Grant

Title: Frontotemporal dementia-like symptoms and axon initial segment pathology in the C9orf72 (C9-500) BAC mouse model

Authors: *Z. ZHAO[1], S. DRÆBY[1], S. S. KAALUND[2], C. F. MEEHAN[1];
[1]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark; [2]Bispebjerg Hospital, Res. Lab. For Stereology and Neurosci., Copenhagen, Denmark

Abstract: Frontotemporal dementia (FTD) is an early onset dementia, preferentially affecting the frontal and temporal lobes. This results in behavioral and personality changes as well as difficulties in language and memory. FVB/NJ- Tg(C9ORF72*)500Lpwr/J) mice contain the most frequently reported mutation found in both familial and sporadic FTD and ALS, this being non-coding repeat expansions in the C9ORF72 gene. The mice exhibit TDP-43 pathology, characteristic of these diseases and show incomplete penetrance of motor symptoms by around 200 days of age. In our experiments, we have now been investigating possible FTD-like behavioural changes in older C9orf72 $^{(+/-)}$ female mice. From 200 to 400 days old we performed behavioural tests at 50-day intervals, including the three-chamber sociability test, the marble burying test, the light dark test and open field tests. Using these tests, we found that a surprisingly high number of C9orf72 mice (~50%) develop an FTD-like phenotype by around 350 days age, characterized by antisocial behaviour, apathy, and reduced self-grooming. None of the wild type littermates developed these symptoms. Stereological cell counting in the frontal lobes revealed only minimal neuron loss in the frontal lobes of the C9orf72-FTD mice. Consistent with this, structural MRI scanning of the brains did not show a significant reduction in frontal cortical volume in C9orf72-FTD mice when normalized to the total brain volume. We thus presumed that cellular dysfunction must be driving the functional changes in the mice.

Immunohistochemical labelling of axonal initial segments of neurones in the frontal lobes revealed that they were longer in the C9orf72-FTD mice than both WT mice and C9orf2 mice without FTD-like symptoms. The structural integrity of the axonal initial segments was also compromised in the C9orf72-FTD mice showing a breakdown in the proximal border of the axonal initial segments with the soma in many neurones. Additionally, increases in soma size in the C9orf72-FTD mice were observed. In conclusion, we have characterized the progression of FTD-like symptoms in C9orf72-FTD/ALS mice and suggest that axonal dysfunction in the frontal lobes might contribute to these symptoms.

Disclosures: Z. Zhao: None. **S. Dræby:** None. **S.S. Kaalund:** None. **C.F. Meehan:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.18/B118

Topic: C.06. Neuromuscular Diseases

Support: Lundbeck Foundation Ascending Investigator Grant

Title: Aging enhances spinal motoneurone excitability in C9orf72 (C9-500) BAC mice

Authors: *M. G. KOLMOS, Z. ZHAO, A. GNANASAMPANTHAN, V. REHAKOVA, R. ABDI, C. F. MEEHAN;
Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Repeat expansions in the C9orf72 gene (C9orf72 RE) are the most common mutations found in both familial and sporadic Amyotrophic Lateral Sclerosis (ALS). *In vitro* recordings from IPSCs derived from C9orf72 ALS patients have demonstrated an early increase followed by a later decrease in motoneurone excitability suggesting that neurones “crash and burn” in this disease. However, these IPSCs represent embryonic-stage neurones so it is difficult to extrapolate to any kind of disease stage. Additionally, the mutant cells may simply be more vulnerable to *in vitro* conditions. Our previous work investigating motoneurone excitability *in vivo* in mouse models with C9orf72 repeat expansion found relatively normal excitability at around 250 days when mild motor symptoms first appear. As aging is the biggest risk factor for ALS, including in C9orf72 RE carriers, we hypothesized that excitability might be impaired with later aging. To test this, we performed in vivo intracellular recordings from spinal motoneurones in 600+ day old FVB/NJ-Tg(C9orf72)500Lpwr/J mice and age matched- wild type (WT) littermates. We selected mice for this study that had not shown a strong ALS (or FTD) phenotype at around 250 days and thus could be aged until 600+ days. However, tail suspension tests revealed that almost all C9orf72 RE mice (83%) now exhibited a clasping phenotype within 1 minute of suspension at this age. Open field tests did not reveal any changes in locomotor activity in the C9orf72 RE mice, but the C9orf72 RE mice were more likely to have an unkempt apparent making them easily distinguishable from their WT littermates. Our intracellular

recording showed that surprisingly, at this age, rather than decreased excitability, there was a significant increase in the I-f gain and a significant reduction in rheobase in motoneurones in aged C9orf72 RE mice. Preliminary anatomical investigations did not reveal any structural changes in axon initial segments that could explain the excitability changes but a trend for decreased motoneurone soma size was seen. The changes we observed are similar to the excitability profile that we have observed in other ALS mouse models suggesting that advanced aging is necessary to evoke hyperexcitability in this model.

Disclosures: M.G. Kolmos: None. **Z. Zhao:** None. **A. Gnanasampanthan:** None. **V. Rehakova:** A. Employment/Salary (full or part-time):; 2NPharma. **R. Abdi:** None. **C.F. Meehan:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.19/B119

Topic: C.06. Neuromuscular Diseases

Title: Considerations for therapeutic modalities in C9orf72 mouse models of ALS

Authors: *C. T. SMOTHERS[1,2], N. K. TIWARI[3,2], P. B. MARTIN[4], M. F. PRESA[4], M. TERREY[5], M. S. TRUJILLO[6,2], L. P. BOGDANIK[7];
[1]Tech. Information Services, The Jackson Lab., Sacramento, CA; [2]The Jackson Laboratory Mice and Clinical & Research Services, The Jackson Laboratory, Bar Harbor, ME; [3]Tech. Information Group, The Jackson Lab., Sacramento, CA; [4]Rare Dis. Translational Ctr., The Jackson Lab., Bar Harbor, ME; [5]Rare and Orphan Dis. Ctr., The Jackson Lab., Ellsworth, ME; [6]Jax Mice and Clin. Services, Jackson Lab., Sacramento, CA; [7]Preclinical Services, The Jackson Lab., Bar Harbor, ME

Abstract: Amyotrophic lateral sclerosis/Frontotemporal dementia (ALS/FTD) is a progressive, fatal disease characterized by motor neuron degeneration, affecting an estimated 9.9 individuals per 100,000 in the United States. To study this disease and test potential treatments, various mouse models have been generated. Here we present the side-by-side characterization of two distinct models that express a hexanucleotide repeat expansion of the C9orf72 gene. The first model is a transgenic that encodes the human C9orf72 genomic sequence with 100-750 hexanucleotide repeat expansions. Mice hemizygous for the transgene exhibit RNA foci and soluble poly(GP) dipeptides in the cortex, hippocampus, and cerebellum as early as 3 months of age. This model can provide efficacy data for test articles that modulate RNA foci and dipeptides, as well as edit the human genomic sequence.The second model is induced by an adeno-associated virus (AAV) that expresses the repeat expansion only. This model exhibits a more comprehensive ALS/FTD pathophysiology, including RNA foci, dipeptide repeats, TDP-43 aggregation, inflammation, neurodegeneration, elevated serum neurofilament light chain (NFL), and behavioral deficits. These deficits are observed at 6 and 12 months post AAV-

injection. While this model provides a more complete and translational ALS/FTD phenotype, it is limited to non-AAV based therapies or approaches targeting the repeat expansion itself. Gene therapy trials in this model may be impacted by the induction mechanism. In conclusion, the choice of therapeutic modality will determine which model is most suitable for use in preclinical trials.

Disclosures: C.T. Smothers: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **N.K. Tiwari:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **P.B. Martin:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M.F. Presa:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M. Terrey:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M.S. Trujillo:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **L.P. Bogdanik:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.20/B120

Topic: C.06. Neuromuscular Diseases

Title: Developing a new C. elegans and mouse models to study the contribution of antisense CCCCGG transcript in C9ORF72 ALS/FTD pathogenesis

Authors: *N. SHARMA[1], G. GHADGE[2], Y. SONOBE[3], P. KRATSIOS[4], R. P. ROOS[2]; [1]Dept. of Neurobio., The Univ. of Chicago, Chicago, IL; [2]Univ. of Chicago, Chicago, IL; [3]Neurol., Univ. of Chicago, Naperville, IL; [4]Neurobio., Univ. of Chicago, Chicago, IL

Abstract: A hexanucleotide repeat expansion-GGGGCC in the intron of C9ORF72 is known as the primary cause of inherited amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). This expansion leads to the generation of sense (GGGGCC) and antisense (CCCCGG) RNAs, both of which can be toxic. Additionally, these transcripts undergo translation into pathogenic dipeptide repeat (DPR) proteins, including poly-GA, poly-GP, poly-GR from sense RNA, and poly-PA, poly-PR, poly-PG from antisense RNA. DPRs have been detected in neural cells of individuals with C9ORF72 ALS and FTD. Previous research has primarily focused on the sense transcript, but recent failures in clinical trials targeting sense RNA suggest the importance of investigating the contribution of antisense transcript and its DPRs to disease pathogenesis. Hence, there is a critical need for animal models that can differentiate between the roles of sense and antisense transcripts and DPRs in disease development.In this study we aimed to gain a deeper understanding of the contribution of sense and antisense RNA/or DPRs neurotoxicity and thus we have developed two distinct *in-vivo* models- *C. elegans* and *mus musculus* expressing 35 copies of human antisense CCCCGG repeat expansion under ubiquitous promoter (C. elegans) and through intracerebroventricular AAV injection into neonatal mice (P0). Preliminary observations in *C. elegans* with antisense repeats suggest the production of

toxic DPRs (poly-PR, poly-PG), reduced lifespan and altered swimming behavior. In neonatal mice injected with the AAV vector, hindlimb strength deficits were observed in the adult stage, along with the production of toxic DPRs such as poly-PR. Next this *in-vivo* model will evaluate; a) motor neuron defects, b) spatial expression of DPRs at single cell levels, and c) identifying novel regulators necessary for antisense DPRs synthesis. The findings from our study suggest that the antisense CCCCGG transcript and/or its cognate DPRs significantly contribute to C9ORF72 ALS/FTD pathogenesis. By utilizing specific strengths of an invertebrate (C. elegans) and a mammalian (Mus musculus) model system, this study establishes new *in-vivo* models to dissect the underlying pathogenic molecular mechanisms of C9ORF72 ALS/FTD, providing valuable tools for future research in this field.

Disclosures: N. Sharma: None. **G. Ghadge:** None. **Y. Sonobe:** None. **P. Kratsios:** None. **R.P. Roos:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.21/B121

Topic: C.06. Neuromuscular Diseases

Title: Elucidating mechanisms underlying neuron type susceptibility to C9ORF72 ALS

Authors: *I. WEIGLE[1], J. S. MARKMAN[2], Y. CHEN[2], R. P. ROOS[3], P. KRATSIOS[2]; [2]Neurobio., [3]Neurol., [1]Univ. of Chicago, Chicago, IL

Abstract: A key feature of ALS is the progressive loss of upper and lower motor neurons, while many non-motor neurons are spared and remain functional. Many cellular mechanisms in motor neurons are defective in *C9ORF72* ALS, including nucleocytoplasmic transport, RNA function, endoplasmic reticulum (ER) stress, mitochondrial function, ubiquitin-proteasome function, protein transport, neuronal excitability and autophagy. However, additional research is needed to fully elucidate the genetic factors that underlie differential susceptibility of neurons in ALS/FTD. The Kratsios lab has established a *C. elegans* model of *C9ORF72* ALS that recapitulates many disease-associated phenotypes including reduced lifespan, locomotion deficits, dipeptide repeat protein (DPR) production, and age-related loss of motor neurons (PMID:34654821). Preliminary evidence using this model suggests harsh touch response remains intact and certain non-motor neuron populations, such as dopaminergic neurons and premotor interneurons, remain unaffected despite the ubiquitous expression of G_4C_2 repeats, mirroring observations in ALS patients. *C. elegans* strains that express 75 G_4C_2 repeats in a cell-type specific manner have been generated to distinguish cell-autonomous and non-cell-autonomous disease mechanisms, to identify neuron types resistant to degeneration, and to perform a genetic screen to identify factors underlying differential susceptibility. I hypothesize that the pathological effects of G_4C_2 repeat expression are primarily cell-autonomous and that cell type-specific neuroprotective genetic factors confer selective resistance to G_4C_2 repeat-associated neurotoxicity. An unbiased forward genetic screen

will be performed on animals that express 75 G_4C_2 repeats exclusively in touch receptor neurons to identify mutants that visually display enhanced production of poly-GA, the most abundant DPR, and mechanosensory deficits. Whole-genome sequencing coupled with genetic mapping will be employed to identify genetic modifiers that enhance susceptibility to C9ORF72-related toxicity. Identification of factors that prevent non-motor neuron types from degenerating is a crucial first step in developing therapeutic strategies that manipulate protective pathways in vulnerable motor neurons to prevent neurodegeneration.

Disclosures: I. Weigle: None. **J.S. Markman:** None. **Y. Chen:** None. **R.P. Roos:** None. **P. Kratsios:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.22/B122

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: Lundbeck Foundation R434-2023-347
ALS-fonden Denmark

Title: Gene Environment interactions influencing neuronal excitability in C9orf72 ALS

Authors: S. DRÆBY[1], V. REHAKOVA[2], A. GNANASAMPANTHAN[3], K. HOUGAARD[4], *C. F. MEEHAN[2];
[1]Dept. of neuroscience, [2]Univ. of Copenhagen, Copenhagen, Denmark; [3]Psychology and Neurosci., Univ. of St Andrews, St Andrews, United Kingdom; [4]Natl. Res. Ctr. for the Working Envrn., Copenhagen, Denmark

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative condition affecting motoneurones. One of the biggest challenges in developing better treatments for this disease is that, for the vast majority of cases we still do not know what is actually causing the disease. The most common mutations found in both sporadic and familial ALS are non-coding repeat expansions in the C9orf72 gene (C9orf72 REs). However, the penetrance of ALS in patients carrying C9orf72 REs is not 100%, meaning that not every carrier of the mutation develops the disease. This indicates that some external trigger may be necessary to induce disease penetrance in C9orf72RE carriers. Occupations with a high exposure to diesel exhaust particles have a higher risk for this disease, implicating diesel exhaust particles as a potential trigger.
An increased excitability of the motor system has consistently been observed in Amyotrophic Lateral Sclerosis (ALS) patients at both the cortical and lower motoneurone levels, including in C9orf72RE carriers. These changes appear to depend on whether C9orf72RE carriers are symptomatic or not. Therefore, we have begun to explore the impact of environmental factors on neuronal excitability in C9orf72 (C9-500) BAC mice. We initially focused our experiments on C9orf72RE mice that showed a slowly progressing motor phenotype raised in a clean

environment. *In vivo* intracellular recordings from spinal motoneurones were performed at around 250 days of age in the C9orf72 and WT littermates. Most basic excitability parameters such as rheobase, voltage threshold and I-f gain were unchanged, except motoneurones from C9orf72RE mice showed signs of increased persistent inward currents. The changes seen in this model are therefore less extreme than those seen in other ALS mouse models at more advanced disease stages.
Next, we tested the impact of diesel exhaust particle exposure, modelling this by applying 3 x intratracheal instillations of carbon black particles, (a model of diesel exhaust particles) at around 100 days of age. We then measured neuronal excitability 150 days later. Our preliminary results showed that motoneurones in exposed C9orf72 mice show increased spontaneous action potential firing compared to both non-exposed C9orf72 and exposed WT mice. Our results suggest that gene-environment interactions are necessary to induce neuronal hyperexcitability in 250 day-old C9orf72 RE mice.

Disclosures: S. Dræby: None. **V. Rehakova:** A. Employment/Salary (full or part-time):; 2NPharma. **A. Gnanasampanthan:** None. **K. Hougaard:** None. **C.F. Meehan:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.23/B123

Topic: C.06. Neuromuscular Diseases

Title: The PFN1^{C71G} transgenic mouse model recapitulates characteristic ALS features, including TDP-43 proteinopathy and progressive motor neuron degeneration

Authors: *X. LI, Y. GU, D. BODNAR, Y. LUO, D. FERRETTI, R. DRISCOLL, D. Y. KWON;
Biogen, Cambridge, MA

Abstract: Mutations in Profilin 1 (PFN1) cause amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease characterized by the loss of upper and lower motor neurons and the presence of mislocalized, phosphorylated TDP-43 aggregates. A lack of ALS mouse models recapitulating TDP-43 proteinopathy has hindered drug development efforts. Here we performed an in-depth characterization study of a previously published transgenic mouse model overexpressing the ALS-associated mutant protein, PFN1^{C71G}. We observed a Wallerian phenomenon, where neuromuscular junction (NMJ) denervation, muscle atrophy, and elevated levels of blood neurofilament (NfL) preceded significant loss of motor neurons, leading to a reduction in compound muscle action potentials (CMAP) amplitudes and muscle force that preceded signs of motor dysfunction. Notably, we observed an age-dependent rise in insoluble phosphorylated TDP-43 in the spinal cord of PFN1^{C71G} mice that correlated with neurodegeneration. Together, these results indicate that the PFN1^{C71G} transgenic mice can serve as a valuable mouse model for ALS therapeutic development.

Disclosures: X. Li: A. Employment/Salary (full or part-time):; Biogen. **Y. Gu:** A. Employment/Salary (full or part-time):; Biogen. **D. Bodnar:** A. Employment/Salary (full or part-time):; Biogen. **Y. Luo:** A. Employment/Salary (full or part-time):; Biogen. **D. Ferretti:** A. Employment/Salary (full or part-time):; Biogen. **R. Driscoll:** A. Employment/Salary (full or part-time):; Biogen. **D.Y. Kwon:** A. Employment/Salary (full or part-time):; Biogen.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.24/B124

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant RF1AG064822
NS110455

Title: Inoculation of detergent-insoluble PFN1 accelerates the onset and progression of disease in PFN1 transgenic rats

Authors: *T. ZHANG;
Florida Intl. Univ., Port Saint Lucie, FL

Abstract: Emerging evidence points to a pathological gain of function in mutated PFN1, highlighted by the formation of PFN1 aggregates as a significant pathological hallmark in transgenic rat models. The role of protein aggregation in neurodegeneration was further elucidated through the administration of detergent-insoluble extracts from ALS-afflicted, paralyzed rats to asymptomatic recipient rats expressing mutant PFN1. This intervention precipitated the rapid onset of PFN1 inclusions and ALS-like phenotypes, while extracts from wild-type PFN1 transgenic rats failed to produce such effects. These observations suggest that the presence of detergent-insoluble PFN1 in the extracts is instrumental in driving ALS pathology in recipient rats. Notably, administering these extracts to rats already exhibiting PFN1 inclusions did not alter the disease progression, indicating a seeding rather than an augmenting role in initiating neuropathological changes. Moreover, pathogenic PFN1 exhibited increased affinity for the molecular chaperone DNAJB6, sequestering it within protein inclusions and thereby reducing its availability for cellular functions. These findings reveal a novel mechanism underpinning the prion-like characteristics of pathogenic PFN1 in the progression of neurodegeneration in PFN1-related ALS.

Disclosures: T. zhang: None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.25/B125

Topic: C.06. Neuromuscular Diseases

Title: Biomarkers to track disease progression in mouse models of amyotrophic lateral sclerosis, implications for preclinical drug discovery

Authors: *N. K. TIWARI[1], M. S. TRUJILLO[2], P. B. MARTIN[3], L. P. BOGDANIK[4], M. TERREY[5];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and ultimately fatal neurodegenerative disorder characterized by the degeneration of motor neurons within the brain and spinal cord. Blood-based biomarkers are gaining traction for human clinical trials to evaluate new drugs to treat ALS. The identification of biomarkers capable of forecasting disease progression or gauging therapeutic efficacy holds significant promise for enhancing the preclinical evaluation of novel treatments. In our research, we leverage mouse models of ALS to assess such biomarkers. Fluid-based biomarkers, exemplified by Neurofilament light chain (NfL), which are released into the bloodstream by damaged neurons, offer a readily measurable indicator of disease pathology. We have observed a marked elevation in NfL levels within ALS mouse models. Additionally, neurophysiological biomarkers such as compound muscle action potential (CMAP) and Motor Unit Number Estimation (MUNE) afford insight into muscle and neuronal activity. Animal models also enable the assessment of behavioral phenotypes, with assays such as rotarod performance, hanging wire tests, home cage running wheel utilization, locomotion analysis, and gait assessment serving as key metrics in our investigations. Furthermore, post-mortem analyses permit the examination of neuroinflammation and axonal damage. The comprehensive evaluation of these diverse biomarkers holds considerable potential for advancing therapeutic strategies aimed at ameliorating this debilitating disorder.

Disclosures: N.K. Tiwari: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M.S. Trujillo:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **P.B. Martin:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **L.P. Bogdanik:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M. Terrey:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.26/B126

Topic: C.06. Neuromuscular Diseases

Support: NSFC Grant 82271483

Title: Mettl3 regulates the m6a RNA modification of WNT signaling pathway in hSOD1-G93A amyotrophic lateral sclerosis mice

Authors: *J. LIU, Y. GUAN, Y. CHEN, H. ZHANG, Q. SU, S. LV, X. CHEN, H. LE; Shandong Second Med. Univ., Weifang, China

Abstract: Amyotrophic lateral sclerosis (ALS) is a motor neuron disease that causes progressive degeneration of motor neurons (MNs). There is no effective treatment. Studies have found that epigenetics plays an important role in ALS. N6-methyladenosine (m6A) is the most abundant internal modification of eukaryotic mRNA, regulating RNA stability, splicing, degradation, translation and other processes. In our study, we select hSOD1-G93A ALS transgenic mice (ALS mice) at the early-symptomatic phase (95 d), middle-symptomatic phase (108 d) and end-symptomatic phase (122 d), as well as age-matched wild-type littermates (WT mice). Using Liquid chromatography-tandem mass spectrometry (LC-MS/MS) we found that the m6A modification levels in spinal cord of ALS mice at 108 d were significantly decreased compared with WT mice. Next, the expressions of methyltransferase during ALS progression were measured. We found that compared with WT mice, the expression of METTL3 protein in the spinal cord of ALS mice at 95 d, 108 d, and 122 d was reduced, while the expression of METTL14 and WTAP proteins remained unchanged. In addition, the double immunofluorescence staining results showed that m6A and METTL3 co-expressed with ChAT positive MNs in the spinal cord of ALS and WT mice. Moreover, m6A and METTL3 immunoreactivity were reduced in ALS mice compared with WT mice. We previously found that the WNT signaling pathway plays a crucial role in the pathogenesis of ALS. m6A modification can affect WNT signaling molecules and participate in disease progression. After overexpression of *Mettl3* in hSOD1-G93A mutant NSC34 cells, increased mRNA m6A levels were observed using dot blot. Meanwhile, *Wnt5a* mRNA levels decreased after *Mettl3* overexpression. The SRAMP analysis indicated that there is m6A methylation modification sites in *Wnt5a* mRNA. Based on these results, we speculate that METTL3 mediated m6A RNA modification may participate in ALS motor neuron degeneration by regulating the WNT signaling pathway. The specific mechanism will be further studied.

Disclosures: J. Liu: None. **Y. Guan:** None. **Y. Chen:** None. **H. Zhang:** None. **Q. Su:** None. **S. Lv:** None. **X. Chen:** None. **H. Le:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.27/B127

Topic: C.06. Neuromuscular Diseases

Support: Fond de recherche Santé Québec - 336802

Title: Calpastatin compensation restores motor neurons and synaptic transmission at NMJs inC9orf72 ALS

Authors: *L. LESCOUZÈRES[1,2], Z. BUTTI[3], M. CHAINEAU[2], T. M. DURCAN[2], K. PATTEN[1,4];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects motor neurons, resulting in progressive paralysis of the muscles involved in voluntary movement. Identification of novel therapeutic targets and treatments are desperately needed for ALS. Recently, an expansion of a hexanucleotide repeat (GGGGCC) in the first intronic region of the C9orf72 gene was discovered as the first genetic cause of ALS. To investigate the role of loss of function of the C9orf72 gene in ALS, the laboratory has developed a zebrafish C9orf72 model (C9-miRNA). This model reproduces the severity of muscle atrophy, motor and synaptic defects observed in patients, and is characterized by a strong decrease in the expression of the calpastatin protein (CAST). In this study, we showed that the addition of Calpeptin and calpastatin active peptide, two coupounds restoring calpastatin function, is sufficient to rescue the locomotor and neuromuscular phenotype of the C9-miRNA model. Also, both synaptic vesicle turnover and release of quantal synaptic vesicles at the neuromuscular junction were restored. We are currenlty investigating the therapeutic and neuroprotective potential of CAST in iPSc models of patients with C9orf72 mutations, differentiated into motor neurons. This approach, combined with single-cell RNA sequencing (scRNA-seq), could open several avenues about pathogenesis and therapeutic intervention associated with the C9ORF72 gene mutation in ALS.

Disclosures: L. Lescouzères: None. **Z. Butti:** None. **M. Chaineau:** None. **T.M. Durcan:** None. **K. Patten:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.28/B128

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R15NS120154
G-RISE T32GM144895
COBRE 5P20GM103653
RISE R25GM122722

Title: Presymptomatic cellular and structural pathologies in the cerebellum of the SMNΔ7 mouse model for Spinal Muscular Atrophy

Authors: *N. C. COTTAM[1], M. A. HARRINGTON[2], C. GROVER[2], J. SUN[2];
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Abstract: Presymptomatic cellular and structural pathologies in the cerebellum of the SMNΔ7 mouse model for Spinal Muscular Atrophy
Nicholas Cottam, Morgan Dowling, Melissa Harrington, Cam Grover, Jianli Sun Delaware State University
Spinal Muscular Atrophy (SMA) is a disease that affects 1 in every 6,000-10,000 individuals at birth, making it the leading genetic cause of infant mortality. SMA is best defined by motor neuron dysfunction due to a deletion or mutation in transcripts of survival motor neuron protein (SMN), which leads to degeneration and dysfunction in the anterior horn of the spinal cord. However, SMN is a ubiquitous protein with a broad range of cellular functions, thus SMN protein deficiencies cause broad complications. Our previous studies investigating the SMNΔ7 mouse model of SMA reported late stage (postnatal day 12) structural and functional defects in the cerebellum of SMA-affected mice. However, it remains unknown whether the cerebellum primarily contributes to the pathology of SMA. In this study, we investigated early stage (postnatal day 3-4) structural and cellular pathology in the cerebellum of SMA-affected mice using diffusion tensor imaging (DTI) with tractography and a lobule-specific immunohistochemical analysis. At this presymptomatic age, cerebella displayed disproportionately lesser volume than the rest of the brain. However, white matter pathways are unaffected, albeit DTI tract accuracy may be limited at this age. Interestingly, Purkinje cell counts and densities are higher in SMA vermis compared to control, but not the hemispheres. Astrocytic reactivity, measured by glial fibrillary acidic protein (GFAP) expression, was similar across SMA and control in the lobules, deep cerebellar nuclei, and white matter. SMA-affected vermis showed more pronounced foliation, while the lobular microstructure within SMA-affected cerebella was also not significantly different compared to controls. These results showed that the postnatal development of the cerebellum is being disrupted by SMA, and that Purkinje cells are a cell type that appear particularly vulnerable. The structural and cellular pathology observed at presymptomatic stages of SMA mice in this study suggest that the defects of the cerebellum may primarily contribute to the pathology of SMA.

Disclosures: N.C. Cottam: None. **M.A. Harrington:** None. **C. Grover:** None. **J. Sun:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.29/B129

Topic: E.09. Motor Neurons and Muscle

Support: NIH grant- R01NS113141
NIH grant- R01NS121618

Title: Alanine-enriched diet ameliorates motor deficits in GPT2-null mice: pre-clinical evidence for supplement treatment in a childhood neurometabolic disorder

Authors: *G. KUMAR[1,2], Q. OUYANG[1,2], Y. LIU[3], K. BRADLEY[3], M. SCHMIDT[3], E. M. MORROW[1,2];
[1]Ctr. for Translational Neurosci., Robert J. and Nancy D. Carney Inst. for Brain Sci. and Brown Inst. for Translational Sci., Brown Univ., Providence, RI; [2]Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI; [3]Dept. of Mol. Biol., Cell Biol. and Biochem., Brown Univ., Providence, RI

Abstract: Motivation: Glutamate Pyruvate Transaminase 2 (*GPT2*), located within the mitochondria, plays a pivotal role in replenishing intermediates of the tricarboxylic acid (TCA) cycle. Recessive loss-of-function mutations in the *GPT2* gene are associated with impairments in postnatal brain growth, intellectual and motor disabilities (Ouyang et. al., 2016). Our previous study has demonstrated that reduced neuronal alanine levels in *Gpt2*-null mice correlate with diminished neuronal survival and impaired motor function (Baytas et al., 2022). Hence, we aimed to explore the mechanisms underlying the impact of *Gpt2* mutations on the degeneration of lower motor neural circuit and evaluate the therapeutic potential of an alanine-enriched diet in *Gpt2*-null mice. **Method:** *Gpt-2* heterozygous mice treated with 10% alanine enriched diet (10A), or regular diet (RA) were used for breeding. Wild-type and *Gpt2*-null mice were continued on 10A or RA diet after weaning and checked the survival. Motor behaviors were tested on postnatal day 28 (P28) to P35 using open field, narrow beam walk and footprint walking tests. Compound muscle action potential (CMAP) amplitude of gastrocnemius muscle (GCM) and nerve conduction velocity (NCV) of sciatic nerve (SN) were assessed. Subsequently, ventral horn motor neuron morphology of lumbar spinal cord, axon quantification and myelin basic protein (MBP) of SN, GCM weight, number of muscle fibers and neuromuscular junction (NMJ) quantification were examined. One-way ANOVA and student t-test were used for statistical analysis. **Results:** *Gpt2*-null mice on 10A-diet exhibited extended survival, significantly increased body weight and improved motor function as evident by increased distances traveled in open field, reduced transverse latency in narrow beam walk, and increase ataxia coefficient in the footprint test as compared with *Gpt2*-null mice on RA-diet ($p<0.01$). Electrophysiology tests showed increased CMAP amplitude of GCM and NCV of SN in *Gpt2*-null mice on 10A-diet as compared to RA-diet ($p<0.01$). Histological examinations showed partial restoration of lumbar motor neurons, increased axon numbers and myelination in SN, increased GCM weight, normal muscle morphology with increased myofiber numbers, increased nerve fiber innervation in the motor endplate (NMJ) of *Gpt2*-null mice on 10A-diet as compared with *Gpt2*-null mice on RA-diet ($p<0.05$). **Conclusion:** Our findings unveiled that GPT2 is essential for neuronal metabolism to maintain the integrity of the motor neural circuit. Dietary supplementation with alanine holds promise as a therapeutic approach for treating the symptoms associated with *Gpt2* mutations.

Disclosures: G. Kumar: None. **Q. Ouyang:** None. **Y. Liu:** None. **K. Bradley:** None. **M. Schmidt:** None. **E.M. Morrow:** None.

Poster

PSTR108: ALS and Other Motor Neuron Diseases: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.30/B130

Topic: C.06. Neuromuscular Diseases

Support: Girotondo Onlus
Grant for Internationalization (D13C22001930001)

Title: Unravelling the contribution of mitochondrial SMN1-anticorrelated genes in determining early symptomatic glycinergic system alterations in Spinal Muscular Atrophy

Authors: *A. CARETTO[1], F. DI CUNTO[1], S. E. VARGAS ABONCE[2], A. L. PROCHIANTZ[2], M. M. BOIDO[1], A. E. VERCELLI[1];
[1]Neurosci. Inst. Cavalieri Ottolenghi, Dept. of Neuroscience, Univ. of Turin, Orbassano (TO), Italy; [2]Biol., Col. de France, Paris, France

Abstract: Spinal Muscular Atrophy (SMA) is a progressive neurodegenerative disorder characterized by lower motor neuron (MN) loss, alongside peripheral alterations, caused by mutations/deletion of *Survival Motor Neuron 1* (*SMN1)* gene. Despite the recent advancements in gene-based therapies, significant limitations persist, needing the exploration of novel treatment avenues. Recent insights linking SMA with mitochondrial dysfunctions across various neurodegenerative diseases have highlighted mitochondria as promising therapeutic targets for SMA. In this context, through bioinformatic analysis, we identified 8 human mitochondrial genes significantly anticorrelated with *SMN1* expression. Subsequent investigation led us to focus on *Gcsh*, a gene encoding a mitochondrial subunit of the glycinergic cleavage system (GCS). Indeed, rt-PCR analysis in SMNdelta7 mouse tissues (brain, spinal cord, heart, quadriceps and gastrocnemius; both males and females) revealed significant upregulation of *Gcsh* in the lumbar spinal cord at an early symptomatic stage of the pathology (postnatal day 5, P5), in comparison to control wild-type mice (WT; 6 WT vs 6 SMA, p=0.028). Western blot analysis conducted on the same samples and on *Smn*-siRNA silenced NSC34 cells differentiated in MNs demonstrated an increase in GCSH protein levels. Additionally, RNA-Scope ISH revealed a significant elevation of *Gcsh* in SMA MN soma (3 WT vs 4 SMA, p=0.0003). Immunofluorescence staining on fixed lumbar spinal cord slices further corroborated the significant increase of GCSH expression in MN soma from SMA mice, compared to WT (5 WT vs 5 SMA, p= 0.030). Furthermore, a significant downregulation in the expression of the astrocyte glycine transporter (GlyT1: 6 WT vs 5 SMA, p=0.048) and a parallel slight but not significant increase in the presynaptic transporter (GlyT2: 7 WT vs 6 SMA, p=0.081) were observed in P5 SMA mice. Meanwhile, morphological analysis of Renshaw Cells, key glycinergic interneurons involved in MN recurrent inhibition, unveiled progressive shrinkage between P5 and late P12 stages in SMNdelta7 mice (P5: 3 WT vs 3 SMA, cell soma area p=0.0009, dendrite length p=0.109; P12: 3 WT vs 3 SMA, cell soma area p=0.048, dendrite length p=0.036). Overall, these results suggest SMA-associated alterations in glycine metabolism and potential recurrent inhibition loss, leading to MN hyperexcitability and subsequent degeneration. Further investigation in GCS expression in MNs but also in astrocytes, as well as

glycinergic pathway analysis, will be fundamental for elucidating the role of mitochondria in SMA pathogenesis and identifying novel therapeutic targets for complementary SMA therapies.

Disclosures: A. Caretto: None. **F. Di Cunto:** None. **S.E. Vargas Abonce:** None. **A.L. Prochiantz:** None. **M.M. Boido:** None. **A.E. Vercelli:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.01/B131

Topic: C.08. Ischemia

Support: KBRI basic research programs 24-BR-02-01
KBRI basic research programs 24-BR-03-03
National Research Foundation of Korea (NRF) funded by Ministry of Science and ICT 2021R1A2C1094645

Title: Morphological cell pattern in the penumbral region in neonatal stroke

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Abstract: Neonatal stroke is a significant cause of mortality, severe developmental delays, spastic cerebral palsy, and cognitive impairment. Despite the developing brain's plasticity and self-repair mechanism, neonatal brain injury can develop lifelong motor and cognitive deficits, and yet there is no effective treatment. The penumbra is the reversibly injured zone surrounding the ischemic core, with depleted electrical activity but preserved ion channels due to hypoperfusion, which makes it a target for the treatment. Penumbra has been studied in different aspects such as a diagnostic target, treatment target for neuroplasticity, neuroprotection, and neurorepair, but still cellular and molecular mechanisms remain elusive. In this study, we developed a neonatal stroke model by transient middle cerebral artery occlusion (tfMCAO) in postnatal day 7 mice and sacrificed 4 hours after the procedure. The stroke was validated in the neocortex, striatum, and hypothalamus by TTC and cresyl violet staining. By immunostaining, we obtained an expression profile of several cell markers in the ischemic core, penumbral, and intact areas. Cell proliferation and apoptotic markers were expressed in the penumbral area as well. Noticeably, we observed positive progenitor cell markers in the penumbral area compared to the ischemic core and the intact area. Our study demonstrates that the identification of the positive progenitor cell markers in the penumbral area will be valuable for investigating the function of dynamics, response to injury, and self-regeneration potential within the neonatal

brain, which can give new insight into the pathological mechanism different from the adult brain, and further, it could give a new approach into the treatment of the neonatal stroke.

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.02/B132

Topic: C.08. Ischemia

Support: Nasjonalforeningen for folkehelsen 35364

Title: Immediate responses in the neonatal hippocampus to hypoxia and ischemia: Insights from integrated snRNA-seq and immunohistochemistry

Authors: A. IANEVSKI, W. WANG, M. CAMARA-QUILEZ, J. GRINI, D. S. DØSKELAND, M. BJØRÅS, ***J. YE**;
Dept. of Clin. and Mol. Med. (IKOM), Norwegian Univ. of Sci. and Technol. (NTNU), Trondheim, Norway

Abstract: The neonatal hippocampus, being immature and developing, is particularly vulnerable to hypoxic and ischemic insults, which can significantly disrupt neurogenesis and cellular function. However, the immediate molecular and cellular responses to such conditions remain poorly understood. This study employs an integrated approach, combining single-nucleus RNA sequencing (snRNA-seq) with cutting-edge split-pool combinatorial barcoding technology and immunohistochemistry (IHC) to explore immediate responses in the neonatal hippocampus within three hours post hypoxic and ischemic events. Both the snRNA-seq and IHC image datasets were analyzed using machine-learning-based strategies. Integration of large-scale public datasets comprising over 420,000 cells, processed using advanced machine learning techniques, enabled accurate identification and annotation of 22 distinct cell populations in the mouse hippocampus. Immunohistochemistry was used to validate and spatially map the observed molecular changes. Our study identified a significant rise in activated astrocytes and microglial populations, indicating rapid and effective neuroprotective adaptations. This glial activation coincided with the upregulation of several key pathways, notably the ribosome biogenesis pathway in neuronal populations. In addition, we revealed a significant decrease in mature neuronal populations such as CA neurons and DG granule cells, whereas, immature DG neurons exhibited remarkable resilience, suggesting a developmental stage-dependent variability in response to hypoxia-ischemia. Furthermore, to support ongoing and future hippocampal research, we have made our machine learning-based model available as a web application. When applied to public scRNA-seq hippocampal datasets, this tool not only enhanced the accuracy of cell type annotations but also corrected previously misclassified cell types, thereby facilitating

more precise scientific inquiries into hippocampal function and pathology. This study offers a comprehensive examination of the immediate impact of hypoxia and ischemia on hippocampal cell types, highlighting specific vulnerabilities and adaptive responses crucial for developing targeted therapeutic strategies. Leveraging a comprehensive snRNA-seq atlas along with machine learning-based annotations and immunohistochemistry, this work provides a robust framework for understanding and mitigating the impacts of acute neural injuries.

Disclosures: A. Ianevski: None. **W. Wang:** None. **M. Camara-Quilez:** None. **J. Grini:** None. **D.S. Døskeland:** None. **M. Bjørås:** None. **J. Ye:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.03/B133

Topic: C.08. Ischemia

Support: NIH Grant 4R00NS114166
NIH Grant 1R01NS133434
C.G Swebilius Res TR Uw

Title: Effects of Hypoxic-Ischemic Brain Injury on cell-type cortical network development

Authors: *J. VARGAS ORTIZ[1,2], M. MCNALLY[3,5], D. MCRILEY[6], K. J. STALEY[4,5], A. CHE[7];
[1]Yale Univ., New Haven, CT; [2]Univ. Autonoma de Ctr. America, San Jose, Costa Rica; [3]Massachusetts Gen. Hosp., Charlestown, MA; [4]Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]Harvard Med. Sch., Boston, MA; [6]Psychiatry, Yale Univ. Sch. of Med., New Haven, CT; [7]Psychiatry, Yale Univ. Sch. of Med., new haven, CT

Abstract: Hypoxic-ischemic encephalopathy (HIE) is the most common cause of death and long-term neurological deficits in infants and children. HIE is also the leading cause of neonatal seizures, accounting for 35-45% cases. The most commonly used anticonvulsants for neonatal seizures are GABA receptor agonists such as phenobarbital, which may have adverse developmental effects when used long-term by interfering with interneuron maturation. It is currently unclear whether HIE-induced seizures exacerbate HIE pathology, and how aggressively should neonatal seizures be treated. Clinical efforts are further hampered by limited knowledge on how HIE-induced seizures alter GABAergic interneurons activity. To examine cell-type specific neuronal activity following HIE, we developed a longitudinal *in vivo* 2-photon imaging preparation in combination with the Rice-Vannucci model of HIE in mouse pups expressing GCaMP6s in excitatory (*Emx1-Cre:GCaMP6s*) versus inhibitory (*GAD2-Cre:GCaMP6s*) neurons. Headplates for imaging were implanted at postnatal day (P) 6, and unilateral left carotid artery ligation was performed at P10 followed by 45-min of hypoxia ($Fi0_2$ 8%). Imaging was performed in non-anesthetized mouse pups before ligation, as well as 0, 1, 2,

and 3 hours after hypoxia at P10, then imaged again in the same mice at P11, P12, P14, and P21 to assess longitudinal changes in neuronal activity after HIE. We observed behavioral seizure phenotypes in all HIE mice and an ~36% mortality rate, consistent with previous reports with a similar protocol. Immediately after HIE, we detected persistently elevated calcium levels in both excitatory and inhibitory neurons, followed by cortical spreading depression with a near complete absence of calcium activity in all cells within 30min after HIE. A subset of neurons regained activity by 3 hours post HIE, but network activity remained significantly suppressed. In excitatory neuron network, number of active neurons and levels of network activity remained significantly lower until 3 days after HIE, at P14. Interneuron network activity, on the other hand, returned to baseline levels already at 24 hours post HIE. Our results suggest differential effects of HIE on excitatory versus inhibitory neurons. In addition, our model presents a method to investigate cell-type specific activity following HIE *in vivo* in the developing brain. Understanding how HIE interacts with the maturation trajectory of the GABAergic system during the early postnatal stage will have a significant translational impact on developing therapeutic interventions for HIE and HIE-induced seizures.

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.04/B134

Topic: C.08. Ischemia

Support: HMN 2018/42794
FFU 2021/51833

Title: Parp3 modulates microglia functions in hypoxia-ischemia via proinflammatory mapk pathways

Authors: *M. CAMARA-QUILEZ[1], V. PALIBRK[2], A. BUGAJ[1], K. SCHEFFLER[1], M. BJØRÅS[1], J. YE[1];
[1]IKOM, NTNU, Trondheim, Norway; [2]NTNU, St.Olav Hosp., Trondheim, Norway

Abstract: Perinatal hypoxic-ischemic encephalopathy (HIE) accounts for 25% of developmental pathologies in children. Understanding the events occurring during the acute phase of a stroke is crucial for mitigating the effects. Cell necrosis resulting from HIE triggers phenotypical changes in microglia, including amoeboid morphology, proliferation, and migration toward the damage site. Microglial functionality significantly impacts tissue damage. Oxidative stress from HIE induces DNA damage, activating the DNA Damage Response (DDR). Poly (ADP-Ribose) polymerases (PARPs) are the important DDR signaling molecules. PARP-3, a lesser-known variant, catalyzes mono (ADP) Ribosylation (MARylation), impacting transcription, RNA

processing, cell cycle regulation, and chromatin organization. PARP-3 may regulate proinflammatory mediator production in astrocytes, but its role in HIE immune responses is unclear.
In this study, we used a Parp3-/- mouse model, an experimental disease model of neonatal HIE, and a Parp3-/- human microglia cell line (CHME3) to explore the role of PARP3 in immune responses to hypoxia-ischemia (HI). We revealed increased tissue damage in the Parp3-/- mouse brain, notably in the striatum, within the acute phase (24 hours post-insult). Although we observed uncontrolled microglia proliferation in PARP3-deficient striatum after injury, PARP3-deficient microglia failed to acquire migratory phenotype in response to HI damage. Further analysis in Parp3-/- CHME3 cells revealed abnormal microglial activation and reduced migration ability even under resting conditions. Transcriptome analysis identified differentially expressed genes in Parp3-/- CHME3 cells, particularly highlighting several mitogen-activated protein kinases (MAPKs). Using RT-qPCR and Immunohistochemistry (IHC), we confirmed elevated levels of MAPK11 (also known as P38-MAPK) in Parp3-/- CHME3 cells. In addition, reduced levels of phosphorylated P38-MAPK were observed in the nuclei of Parp3-/- CHME3 cells, indicating altered inflammatory signaling.Our findings indicate that PARP3 is crucial in regulating proinflammatory MAPK pathways, thereby impacting microglia functions and HIE immune responses.

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

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Program #/Poster #: PSTR109.05/B135

Topic: C.08. Ischemia

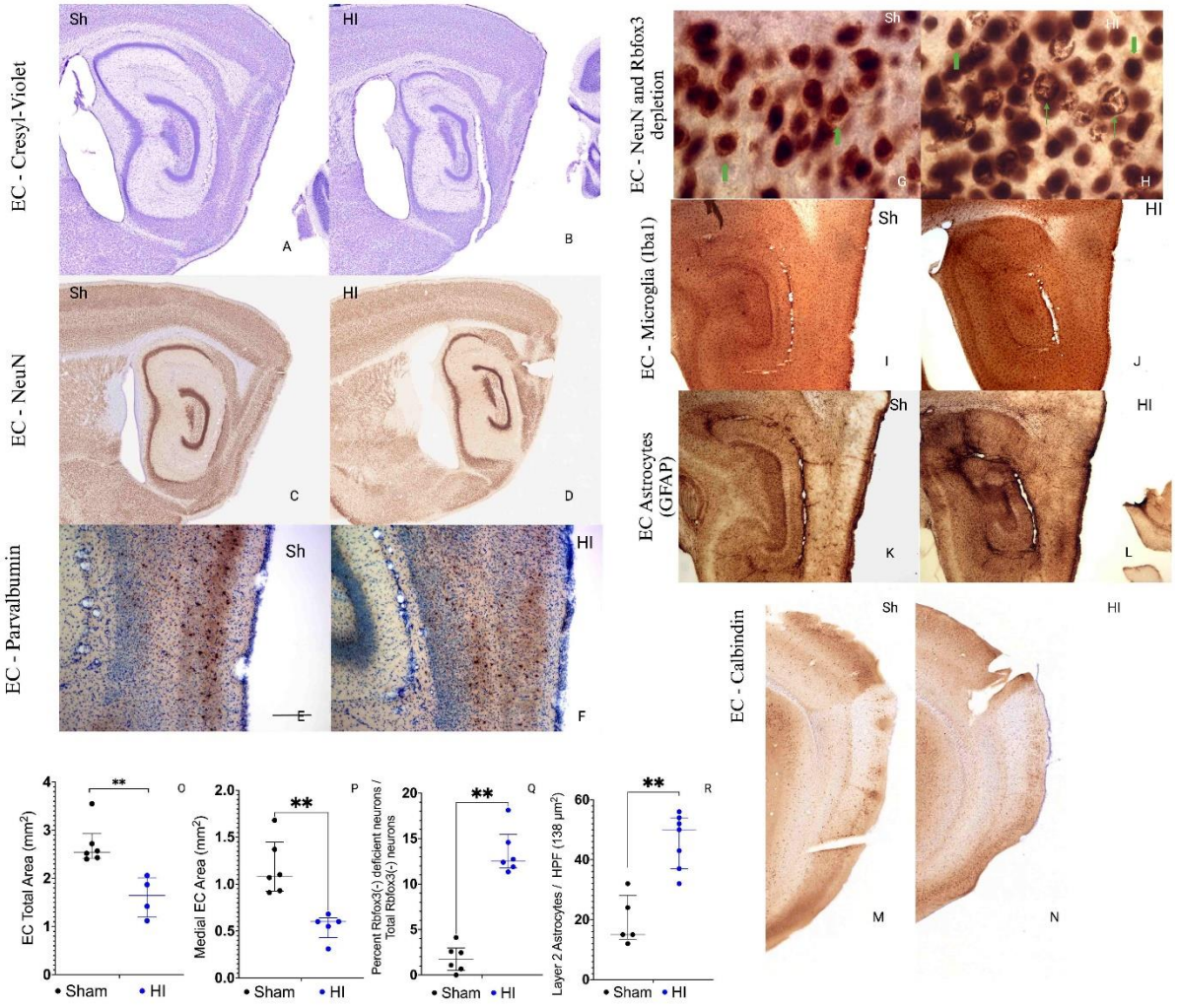
Support: NICHD Grant HD074593
NINDS Grant NS123814

Title: Neonatal hypoxia-ischemia disrupts the adult laminar organization of entorhinal cortex

Authors: B. SOLLINGER[1], ***S. T. COLEMAN**[1], A. CAVANAGH[1], O. HATCHER[1], Z. MAJEED[1], L. J. MARTIN[2], N. KUTER[1], F. J. NORTHINGTON[1];
[1]Div. of Neonatal-Perinatal Medicine, Dept. of Pediatrics, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Pathology, Div. of Neuropathology, Johns Hopkins Univ., Baltimore, MD

Abstract: The entorhinal cortex (EC) relays information in the parahippocampal circuit with Layer 2 (L2) responsible for organizing cortical input to the hippocampus for memory encoding, retrieval, and spatial navigation. Intracortical EC disruption may mediate long-term learning and cognitive consequences of neonatal hypoxic-ischemic (HI) brain injury. Neonatal HI alters EC area, structure, and neural cell laminar organization in the adult brain. C57Bl6 mice subjected to

the Rice-Vannucci model at postnatal day (P)10 with 8% O2 exposure for 45 minutes (n=9), or anesthesia exposed shams (n=11), were perfusion fixed at P180. Cresyl-Violet (CV); GFAP, Iba-1, NeuN, calbindin and parvalbumin (PV) immunohistochemistry was used to detect glia, and total, principal, and inter-neurons. Area and cell counts measured by ImageJ and differences detected with Mann-Whitney analysis; $p<0.05$ considered significant. EC area, specifically medial EC area, was reduced in P180 mice (panels A-F, M-P). Cortical layer organization was disrupted, and neuronal subtypes were aberrant (E,F, M,N). Calbindin 'island and oceans' organization of L2 remained, but island size diminished (M,N). PV+ neuropil (E,F) was lost in L2 and percentage of Rbfox3(-) to NeuN+ neurons decreased (G,H,Q). The clear laminar organization of astrocytes in sham EC (I) was lost following neonatal HI (L,R). No change occurred in Iba-1 expression (J). Neonatal HI alters EC structural organization in adult mice. There was atrophy and aberrant residual lamination, neuronal and glial organization after HI; L2 was particularly sensitive. An anomalous L2 could disrupt cortical input to the hippocampus, effecting memory formation, spatial memory, cerebrovascular perfusion, metabolism, and risk for seizures.



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Poster

PSTR109: Perinatal Ischemia and Hypoxia

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.06/Web Only

Topic: C.08. Ischemia

Support: NIH - Waisman IDDRC P30HD003352
Department of Pediatrics Research & Development Grant
R01NS111021, NIH/NINDS

Title: Sex-specific ntrk2 gene expression in hippocampal interneurons after neonatal hypoxia ischemia

Authors: F. CAMCI[1], N. CAGATAY[1], E. BICKI[1], F. CETIN[1], S. YAPICI[1], A. MADRID[2], P. FERRAZZANO[3], J. E. LEVINE[5], D. M. WERLING[6], A. M. SOUSA[4], *P. CENGIZ[3]; [2]Neurosurg., [3]Pediatrics, [4]Neurosci., [1]Univ. of Wisconsin-Madison, Madison, WI; [5]Neurosci., Wisconsin Natl. Primate Res. Ctr., Madison, WI; [6]Genet., Univ. of Wisconsin, Madison, Madison, WI

Abstract: Background: The hippocampus plays a critical role in learning and memory. Neonatal hypoxia ischemia (HI) related brain injury is a known risk factor for learning and memory deficits in children. Sex-specific outcomes following neonatal HI has been established. We previously showed that there is a sexually differential tyrosine kinase B receptor (TrkB) pathway in the hippocampus post-HI. However, the impact of HI on the individual hippocampal cells and their gene expressions have not been explored. In this study, we aimed to determine the sex differences in gene expression profiles of the individual cell clusters following HI by using single nuclear RNA sequencing and identify the cell types associated with TrkB signaling. **Methods:** Neonatal HI was induced in postnatal day (P) 9 mice using Vannucci's HI model. Ipsilateral hippocampi were extracted 3 days post-HI and variability of the HI injury was controlled by chasing moderately injured hippocampi. Following hippocampal extraction and nuclear isolation, quality control of sequencing was done by FastQC (v0.11.5). Reads were aligned with mouse genome using cell ranger (v6.1.2). Approximately 13,000 nuclei per sequenced sample, with approximately 20,000 reads per nuclei, were associated to approximately 1,300 genes per nuclei. For statistical analysis, R environment (v4.1.2), R package SingleR (v1.8.1), R package Seurat (v4.0.6) were used to identify sex-specific differences for inter-group comparisons for each cluster. An adjusted P-value cutoff was 0.05. **Results:** We identified 44 different hippocampal cell clusters which consisted of 14 glutaminergic and 6 GABAergic neurons, 7 astrocytes, 4 oligodendrocyte precursors, 4 microglia, 2 oligodendrocyte cluster subtypes. Majority of nuclei belong to excitatory dentate gyrus cells. We identified sexually differential gene expressions following HI in excitatory and inhibitory neurons of hippocampus.

Particularly the TrkB gene (Ntrk2) expression has been shown to be increased in female hippocampal inhibitory interneurons specifically in somatostatin (SST) interneurons compared to males post-HI. Ntrk2 expression profiles in SST interneuron clusters are confirmed using RNAscope. Detailed analysis of this large dataset is undergoing. **Conclusion:** Single nuclear RNA sequencing is a promising method to determine the sexually differential pathways activated on different neonatal hippocampal cell clusters. Identifying the cell- and sex-specific pathways associated with gene of interest in our case Ntrk2 gene is important to mitigate the negative effects of HI on the learning and memory.

Disclosures: F. Camci: None. **N. Cagatay:** None. **E. Bicki:** None. **F. Cetin:** None. **S. Yapici:** None. **A. Madrid:** None. **P. Ferrazzano:** None. **J.E. Levine:** None. **D.M. Werling:** None. **A.M. Sousa:** None. **P. Cengiz:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

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Program #/Poster #: PSTR109.07/Web Only

Topic: C.08. Ischemia

Support: NIH - Waisman IDDRC P30HD003352
Department of Pediatrics Research & Development Grant
R01NS111021, NIH/NINDS

Title: Role of membrane estrogen receptor alpha in Trkb mediated sex specific neuroprotection following neonatal hypoxia ischemia: Is there a role for truncated TrkB?

Authors: *F. CETIN[1], N. CAGATAY[2], O. TAPARLI[4], F. CAMCI[2], T. SHEIKH[5], S. YAPICI[3], P. FERRAZZANO[3], J. E. LEVINE[7], P. CENGIZ[6];
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Abstract: Background: Neonatal hypoxia ischemia (HI)-related brain injury leads to learning and memory deficits in children. We previously demonstrated that tyrosine kinase B (TrkB)-mediated neuroprotection is sex specific and dependent on estrogen receptor alpha (ERa) in the hippocampus after neonatal HI. In this study, we hypothesized that sex-specific ERa-dependent and TrkB-mediated long-term neuroprotection is regulated by membrane ERa. To test this hypothesis, we used ERa wild type (WT), ERa complete knockout (ERKO), and nuclear-only ERa (NOER) mice that expresses ERa only in the nucleus to investigate downstream signaling pathways of TrkB and long-term anxiety-like behavior. **Methods**: Postnatal day (P) 9 male and female WT, ERKO, and NOER mice underwent either sham or HI surgery (n=6-10). Mice were given either a vehicle control or a TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF), daily for three or seven days after 10 minutes of HI or sham surgery for subsequent behavioral assessment and

imaging. Hippocampal AKT1/3, ERK1/2, truncated TrkB (T1.TrkB) and full-length TrkB (FL.TrkB) mRNA, and total TrkB (FL.TrkB, T.TrkB), and actin protein expressions were measured at P12. Elevated Plus Maze Testing was performed at P90+, followed by T2 weighted brain MRI. ITK-SNAP was used to calculate hippocampal and hemispheric volume reductions as a percentage. For multi-group comparisons, ANOVA was used. **Results**: Our results show that; 1) HI increases hippocampal AKT1 mRNA but decreases AKT3 mRNA in both WT male and females compared to sham 3 days after HI. 7,8-DHF further increases AKT1 mRNA and reduces AKT3 mRNA expression in female hippocampi after HI ($p< 0.001$). This change of hippocampal AKT1 mRNA and AKT3 mRNA in females is abolished in ERaKO and NOERa mice. HI increases the T1.TrkB mRNA expression and decreases the FL.TrkB expression in WT male and female mice. 2.) HI increases hippocampal T.TrkB protein in both WT male and female mice. 7,8-DHF decreases T.TrkB/actin protein expression only in the female hippocampus post-HI ($p=0.01$). 3) WT female mice spent more time in the open arm post-HI ($p=0.0009$) that is recovered by the 7,8-DHF therapy in an ERa dependent way ($p=0.05$). 4). The % time spent in the open arm positively correlates with the hemispheric and hippocampal injury (R2: 0.42 $p< 0.001$, R2: 0.32 $P< 0.001$). **Conclusion**: Our findings demonstrate that membrane ERa maybe mediating the female-biased TrkB-mediated hippocampal neuroprotection through T.TrkB.

Disclosures: F. Cetin: None. **N. Cagatay:** None. **O. Taparli:** None. **F. Camci:** None. **T. Sheikh:** None. **S. Yapici:** None. **P. Ferrazzano:** None. **J.E. Levine:** None. **P. Cengiz:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.08/B136

Topic: C.08. Ischemia

Support: NIH Grant 1K08N5121599-01
NIH Grant 5R35NS116852-03

Title: Persistently elevated programmed neuronal death after mild perinatal hypoxia-ischemia

Authors: *M. A. MCNALLY[1], L. A. LAU[2], D. HIKE[3], X. LIU[4], X. YU[5], R. DONAHUE[6], J. A. VARGAS ORTIZ[7], A. CHE[8], K. J. STALEY[9];
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Abstract: OBJECTIVE: Mild hypoxic-ischemic encephalopathy (HIE) is common in neonates with 30-40% of patients experiencing adverse long-term outcomes. Progression of injury after

mild HIE is poorly understood, and no therapies are currently available. Thus, we developed a novel in vivo system to measure individual neuronal activity and death in real-time after mild hypoxia-ischemia (HI). METHODS: After P1 intracerebroventricular injection (AAV1-*Syn1*-mRuby2-GCaMP6s) and P8 cranial window placement, P10 mouse pups underwent right carotid ligation and 15 minutes of hypoxia (FiO2 0.08) vs. sham. Chronic, awake 2P calcium imaging of right somatosensory cortex was completed from P10-21. Neuronal death was quantified using the fluorophore quenching assay. Immunohistochemistry and ex-vivo 14T MRI was completed at P28. RESULTS: Mild HI transiently suppresses cortical network activity for hours post-HI (vs. sham, n=13 pups/group; $p<0.01$). No post-HI seizures are seen. By 24 hours, network activity fully recovers and there is no disruption in normal maturational network desynchronization 4 days after HI (n=8 pups/groups; *n.s.*). Cortical activity remains intact for 11 days (n=8 pups/group; *n.s.*). Despite this, mild HI causes delayed, progressive neuronal loss maximal during the second week post-injury (n=8 pups/group; $p<0.01$). At baseline, 1-, 2-, and 4-days post-HI, network participation of individual neurons destined to die is indistinguishable from those that survive (n=8 pups; *n.s.*). 2 weeks post-HI, no cortical or hippocampal atrophy is seen on ex-vivo MRI (n=3 pups/group; *n.s.*). CONCLUSIONS: This is the first study to longitudinally measure neuronal death and network activity in real-time after mild perinatal HI in vivo. Like neonates with mild HIE, our model demonstrated re-constitution of cortical network activity, no post-HI seizures, and no moderate-severe injury. Despite this, neuronal loss is progressive. Critically, the neurons destined to die demonstrate multiple biomarkers of viability for days after injury, suggesting their later death can be modified. These data have important translational implications for patients with mild HIE. Therapies may need to be deployed at a different time and/or for a different duration compared to those used for moderate-to-severe HIE. This novel in vivo model will permit rapid, quantitative measurements with cellular resolution of the neuroprotective utility versus neurotoxicity of new interventions in future studies.

Disclosures: M.A. McNally: None. **L.A. Lau:** None. **D. Hike:** None. **X. Liu:** None. **X. Yu:** None. **R. Donahue:** None. **J.A. Vargas Ortiz:** None. **A. Che:** None. **K.J. Staley:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

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NIH - NINDS R01NS120322
NIH - NINDS R01NS091242
NIH - NINDS R01NS076715
AHA - 19SFRN3483008
DoD - TP210529

Title: Mitochondrial Cardiolipin Modification in Large and Small Animal Models of Neonatal Hypoxic/Ischemic Encephalopathy

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Abstract: Neonatal hypoxic/ischemic encephalopathy (HIE) as the result of perinatal disruption of oxygen delivery to the brain and is the cause of approximately 1 million deaths per year. Surviving infants suffer irreversible neurological damage contributing to developmental abnormalities such as cognitive and motor impairments including cerebral palsy. While reinstating blood flow and oxygen delivery is pertinent for survival, it induces a secondary form of injury termed reperfusion injury. Reperfusion injury produces excessive amounts of reactive oxygen species (ROS) and creates a highly oxidative environment within the mitochondria. When exposed to oxidants, such as ROS, lipids undergo peroxidation which can disrupt their structural integrity. There are several lipids that when oxidized are thought to contribute to reperfusion injury, specifically cardiolipin (CL). CL is found on the inner mitochondrial membrane where it plays integral roles in cellular respiration and cristae structure. Following oxidative stress, CL is externalized to the outer mitochondrial membrane where it is suggested to play a pivotal role in mitophagic flux and cell death signaling cascades. Additionally, CL biosynthesis produces a premature form of CL before converting it to its final, mature form. During this remodeling process, monolysocardiolipin (MLCL) is produced as an intermediate. The purpose of this study is to investigate CL remodeling and MLCL accumulation as a potential therapeutic target for neonatal HIE. In our clinically relevant piglet model, we have observed an accumulation of MLCL following HIE. Additionally, our rodent model demonstrates that CL remodeling and MLCL accumulation to occur in the early phases of reperfusion. Our *in vitro* model of oxygen glucose deprivation and reoxygenation follows this same trend. Taken together, our data suggests this remodeling pathway and MLCL accumulation to play a role in injury progression in cell models of ischemia/reperfusion, and in small and large animal models or HIE. We hypothesize MLCL accumulation contributes to mitochondrial dysfunction and inhibition of this accumulation could provide neuroprotection. Further studies will utilize novel transgenic rodent lines to target MLCL accumulation, visualize its impact on mitochondrial morphology and evaluate its role in white matter injury and behavioral outcomes. *In vitro* studies will allow us to further investigate the mechanism at which these changes are occurring. Together, these studies demonstrate CL remodeling and MLCL accumulation to be translationally relevant to neonatal HIE injury and pose as a potential therapeutic target.

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.10/B138

Topic: C.08. Ischemia

Title: Accumulation of lipid droplets in microglia following hypoxia-ischemia in neonatal brain

Authors: *C. YEN[1], F. LU[2], D. M. FERRIERO[2], X. JIANG[2];
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Abstract: Background: Phagocytic clearance of apoptotic neurons is a core function of microglia following hypoxia-ischemia (HI) in the neonatal brain. Microglia face substantial metabolic stress upon phagocytosis, during which they are overloaded with lipids released from fragmentized membranes, damaged synapses and myelin. Excess intracellular lipids are stored in lipid droplets (LD), the unique organelles that are crucial for lipid and energy metabolism in cells exposed to various stresses including oxidative stress. Recent literature suggests that LD accumulation skews microglia toward a dysfunctional proinflammatory phenotype in the aging brain; and the aged lipid-laden microglia show impaired immune responses to stroke. The presence and function of LD in brain cells after HI in the developing brain are unknown.
Methods: Postnatal day 10 (P10) mice were subjected to HI using the Vannucci model. LD accumulation was demonstrated by the staining of oil red O (ORO) and a florescent probe for neutral lipids BODIPY^{TM} 493/503. Cellular distribution of LD was determined by double immunofluorescent staining with antibodies against perillipin-2 (Plin2), the best-characterized LD resident protein, paired with anti-NeuN, GFAP or Iba1/CD68 antibodies. Additionally, we stained brain sections from patients with hypoxic-ischemic encephalopathy (HIE) for the presence of LD in human brain cells.
Results: At 3-7 days after HI, the ORO staining was evident at the injured regions in the ipsilateral hemisphere. The pattern of ORO staining corresponded to the areas of cell loss in the cortex and hippocampus. Plin2 was localized in CD68-positive microglia/macrophages, but not in neurons and astrocytes. Consistently, LD-accumulating microglia were observed in HIE brains.
Conclusions: Lipid droplets accumulate in activated microglia in HI-injured brain regions in neonatal mice, and in HIE brain as well. Further investigation is aimed to elucidate whether sustained LD accumulation impairs key functions of microglia, and is associated with chronic inflammation following neonatal hypoxia-ischemia.

Disclosures: C. Yen: None. **F. Lu:** None. **D.M. Ferriero:** None. **X. Jiang:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: C.08. Ischemia

Support: Department of Pediatrics Research & Development Grant
NIH/NINDS R01 NS111021
NIH 5UL1TR002373-02

Title: Hypoxia and ischemia induces sexually differential hippocampal corticosterone content in neonatal mice

Authors: *T. VALDES ARCINIEGA[1], F. CETIN[1], I. ISIK[1], N. CAGATAY[1], B. OZAYDIN[2], S. YAPICI[1], L. COLLO[3], P. FERRAZZANO[1], J. E. LEVINE[4], A. KAPOOR[3], P. CENGIZ[1]; [1]Pediatrics, Univ. of Wisconsin-Madison, Madison, WI; [2]Neurosurg., Univ. of Wisconsin-Madison, Madison, WI; [3]Neurosci., Univ. of Wisconsin-Madison, Madison, WI; [4]Neurosci., Wisconsin Natl. Primate Res. Ctr., Madison, WI

Abstract: Neonatal hypoxia-ischemia (HI) related encephalopathy is a major cause of learning/memory deficits. Previous data indicates that male newborns are twice as susceptible to HI, yet the underlying mechanisms remain unclear. Emerging evidence suggests that locally produced sex steroids regulate many functions within the brain following injury. The brain synthesizes and metabolizes steroids, contributing to sexual differentiation and modulation of various neural processes. Neural aromatase activity and subsequent estradiol (E_2) production has been linked to regulation of neurogenesis, synaptic plasticity, neurotransmission, memory, and behavior. While brain-derived E_2, primarily activated by astrocytic aromatase, is an important mediator of neuroprotection, neonatal testosterone (T) may exacerbate HI-induced brain injury. We hypothesize that the sex differences of HI outcomes are due to alterations in hippocampal neurosteroids. Here we investigate male and female neonatal hippocampal neurosteroid contents at 2 time points post-HI, revealing insights into neurosteroid dynamics. HI was induced at postnatal (P) day 9 in C57BL/6J mice (adrenals and gonads intact) using Vannucci's HI model. Sham P9 mice underwent anesthesia and manipulation of the left common carotid artery. We harvested ipsilateral hippocampi on days 1 (P10) and 3 (P12) post-HI (n=1 pooled from 2 mice hippocampi). Blood samples were collected on day 1 and 3 post-HI. LC-MS/MS was used to determine E2, T, progesterone (P4), and corticosterone (CORT) hippocampal contents. Hippocampal hormone data (except T) were winsorized. E_2 and P_4 contents were log-transformed. Data were analyzed by multifactorial ANOVA (condition×day×sex) and shown as mean ± SEM (n=6-9). Plasma steroid levels at P12 did not significantly differ between experimental groups but were lower than hippocampal levels. P10 serum analysis pending. Male hippocampal T content was higher (P=0.01) at P12 (sham, 1852 ± 570; HI, 2455 ± 425 pg/g) compared to P10 (sham, 409 ± 115; HI, 186 ± 61 pg/g). HI-females exhibited lower T levels at P12 than HI-males (P=0.01). Male hippocampal P4 content was higher (P=0.007) at P12 [3.068 ± 0.13 log(pg/g)] vs. P10 [2.31 ± 0.17 log(pg/g)] post-HI. Male hippocampal CORT content at P12 was higher (P=0.004) in HI vs. sham mice. Interestingly, CORT content at P12 post-HI was lower (P=0.05) in females than males. Our results showed sex-specific differences in hippocampal testosterone (T) and corticosterone (CORT) levels post-hypoxia-ischemia (HI). Also, hippocampal neurosteroid levels were not dependent of circulating sex hormones in gonadally and adrenally intact sham and HI mice.

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.12/B139

Topic: C.08. Ischemia

Support: NICHD HD074593
NINDS NS123814

Title: Perforant path neuron injury yields hippocampal denervation correlating with cognitive impairment in adult mice with neonatal hypoxia-ischemia

Authors: *A. S. CAVANAGH[1], B. I. SOLLINGER[1], S. T. COLEMAN[1], O. D. HATCHER[1], N. KUTER[1], L. J. MARTIN[2], F. J. NORTHINGTON[1];
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Abstract: Background: Neonatal hypoxia-ischemia (HI) injures the cerebral cortex and confers permanent memory impairment. The perforant path, arising from the entorhinal cortex (EC) and terminating in the hippocampal dentate gyrus (DG), mediates spatial and episodic memory formation. We hypothesized that neonatal HI brain injury damages perforant path neurons and denervates their hippocampal targets in mice.
Methods: Postnatal day (P) 10 mice (n=14 HI, 11 Sham) were subjected either to the Rice-Vannucci model of HI or only to anesthesia. Mice underwent daily touchscreen behavioral testing, beginning at P70, including a visual discrimination (VD) learning and memory task. Brains were perfusion-fixed at P200 and sectioned sagittally at 50μm. Immunohistochemistry identified principal perforant neurons in EC layers 2/3 by calbindin (CB) and reelin (RE), EC inhibitory interneurons by parvalbumin (PV), and axon terminals in the DG molecular layer (ML) by synaptophysin (SYP). ImageJ was used to quantify neuron number and soma area and SYP integrated density (ID). Unpaired t or Mann-Whitney tests, for intergroup differences, and Pearson or Spearman correlations, for nonlinear regression analyses, were used for normal and non-normal data, respectively, with $p<0.05$ considered significant.
Results: Medial EC (MEC) and lateral EC (LEC) principal and interneurons were deleted by HI (Fig. 1c,d,h,i,l,m) with a decrease in soma area of remaining neurons (Fig. 1e,n). SYP ID in the ML of suprapyramidal (SPB) and infrapyramidal (IPB) blades of the DG was depleted with HI (Fig. 1q,r). HI increased number of sessions to pass the VD task (Fig. 1t). Principal neuron number directly correlated with DGSPB SYP ID (Fig. 1s) which inversely correlated with number of sessions to pass the VD task (Fig. 1u).
Conclusions: Neonatal HI yields damage to mouse EC-hippocampus circuitry correlating with

learning and memory impairment. A mouse model of neonatally acquired HI brain injury with damage to the adult perforant path will be useful to interrogate lifelong circuit-based pathology of complex cognitive impairment.

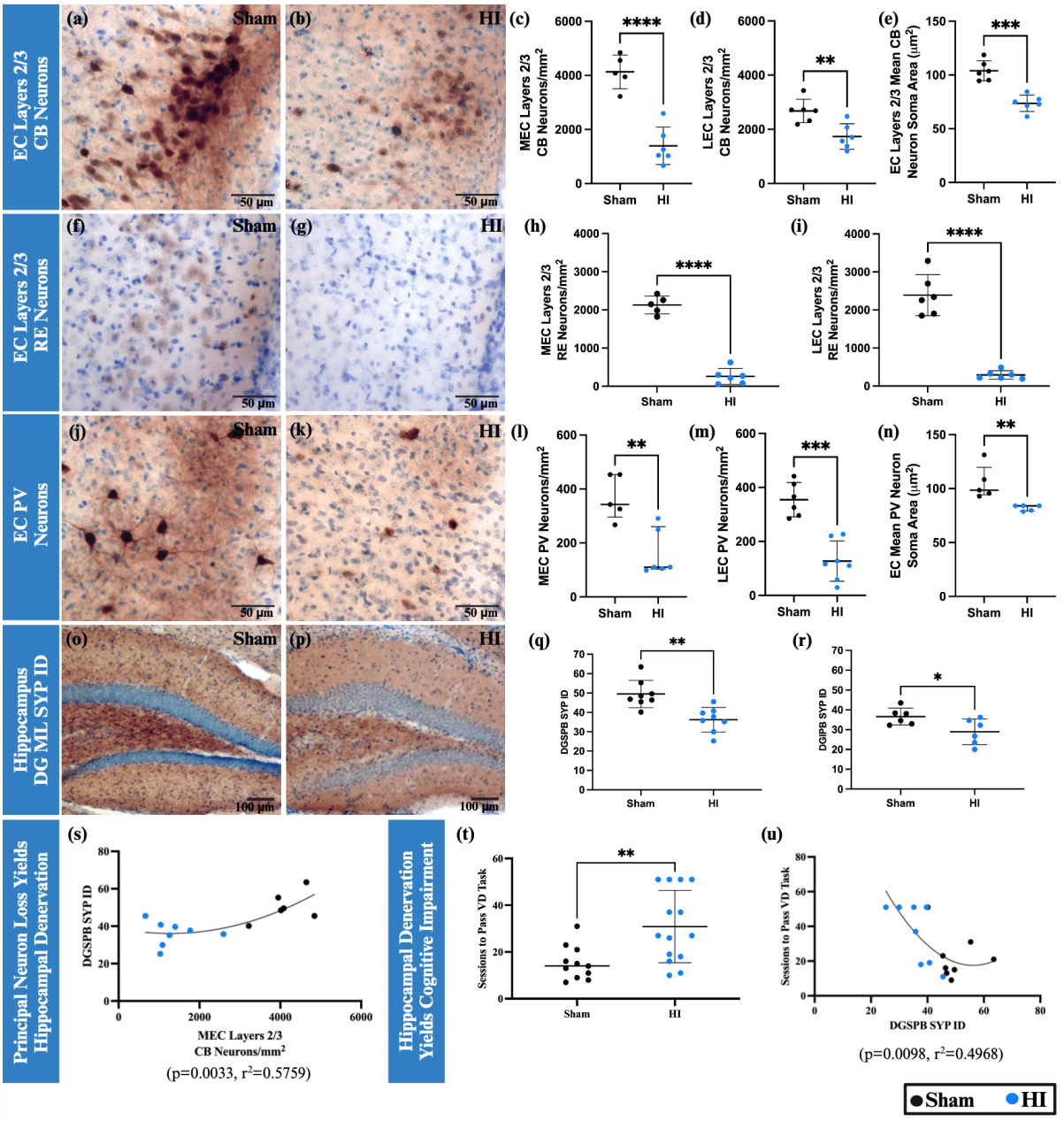

Figure 1. Perforant path neuron injury yields hippocampal denervation correlating with cognitive impairment in adult mice with neonatal hypoxia-ischemia
Created with Biorender.

Disclosures: A.S. Cavanagh: None. **B.I. Sollinger:** None. **S.T. Coleman:** None. **O.D. Hatcher:** None. **N. Kuter:** None. **L.J. Martin:** None. **F.J. Northington:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.13/B140

Topic: C.08. Ischemia

Support: NIH grant 5R01NS117428-03
ANR-INSPIE

Title: Novel Purine Derivative mitigates Hypoxia Ischemia Related Brain Injury through Agrin, Zyxin and Synaptotagmin Proteins

Authors: C. DISDIER[1], A. MAIZA[2], X. CHEN[4], G. VERMA[5], P. GRESSENS[6], B. S. STONESTREET[7], *A. MABONDZO[3];
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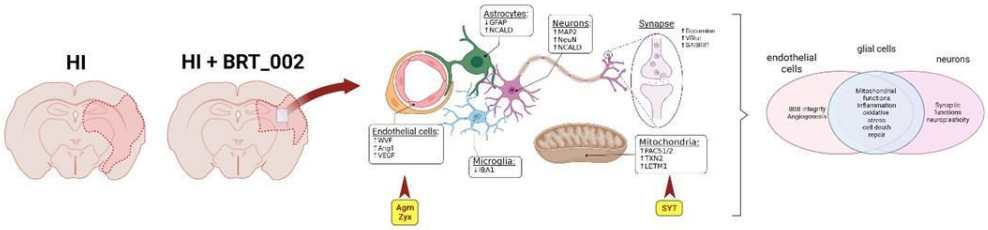
Abstract: Hypoxic-ischemic encephalopathy (HIE) is a major cause of morbidity and mortality in newborns resulting in motor and cognitive impairment. Therapeutic hypothermia is the only approved treatment for HIE, but it is only partially effective. There are currently no pharmacological agents available to treat HIE in newborns. Therefore, it is essential to develop alternative and/or adjunctive novel therapeutic agents to attenuate the sequela resulting from HIE. Some previous approaches have not proven successful possibly in part because they have focused upon discrete aspects of neuropathology originating from hypoxic-ischemic (HI) brain injury such as the neuronal compartment rather than examining potential dynamic interactions within the brain among multiple cellular systems. Given the above considerations, we sought to develop a novel pharmacological agent based on an innovative trisubstituted purine derivative, BRT_002, which potentially could target multiple biological systems and compartments within the central nervous system and attenuate HI-related injury in the neonatal brain. First, safety of BRT_002 was confirmed by treating adult rats with BRT_002 at a high dose (100 mg/kg) for 7-days. Thereafter, the Rice Vannucci model of HI was used to characterize impact of BRT_002 treatment in HI. Sham and HI exposed P7 rats received BRT_002 (30 mg/kg, immediately, 24, and 48 h after HI) or placebo. Pharmacokinetic studies revealed excellent systemic and brain exposure to BRT_002. In addition, treatment with BRT_002 reduced infarct volumes in HI BRT_002 treated animals compared to HI placebo treated animals at 72 h. Shot gun proteomic analyses identified changes in Agrin, Zyxin and Synaptotagmin-5 after treatment with BRT_002. Regulation of Agrin, Zyxin and Synaptotagmin-5 and their interactions could be essential for brain repair by modulating mitochondria functions, preserving neurons, and attenuating inflammation (Figure 1). We conclude that Agrin, Zyxin and Synaptotagmin-5 account for the neuroprotective effects of BRT_002 after HI-brain injury.



Schematic diagram summarizing the major neuroprotective effects of BRT-002 on HI related brain injury in the neonatal rats. BRT-002 exerts multiple beneficial neuroprotective effects in neonatal rats exposed to HI related brain injury. BRT-002 attenuates HI related brain injury as suggested by relative brain tissue preservation. Some of the mechanisms of the neuroprotection potentially include: (1) vascular benefits with relative increases in Agrin and, (2) potential beneficial effects on mitochondrial function as suggested by the *in vitro* OGD studies, (3) potential neuronal preservation and attenuation of inflammation (4) along with potential important interactions among many of these factors

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Poster

PSTR109: Perinatal Ischemia and Hypoxia

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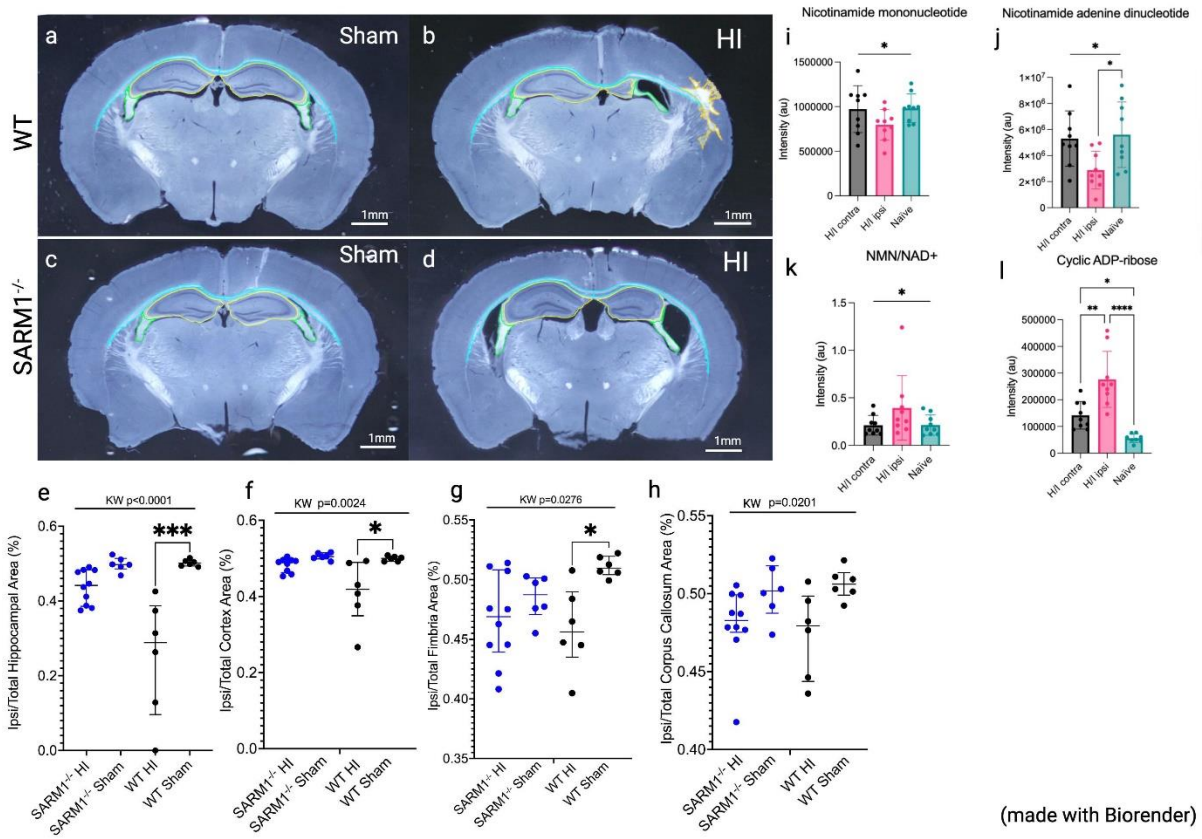
Topic: C.08. Ischemia

Support: NIH Grant HD110091
NICHD Grant HD074593
NINDS Grant NS114144

Title: Sarm1 activation after neonatal hypoxia-ischemia; can it become a new therapeutic target?

Authors: *O. D. HATCHER[1], I. KOUTROULIS[2], N. KUTER[3], B. SOLLINGER[3], A. CAVANAGH[4], S. M. AJA[5], A. EVERETT[3], L. J. MARTIN[6], F. J. NORTHINGTON[7]; [1]Pediatrics, Johns Hopkins Univ., Baltimore, MD; [2]Emergency Med., Children's Natl. Med. Ctr., Washington, DC; [3]Johns Hopkins Sch. of Med., BALTIMORE, MD; [4]Johns Hopkins Med. Institutions, Baltimore, MD; [5]Johns Hopkins Sch. Med., Baltimore, MD; [6]Pathology, Div. of Neuropathology, Johns Hopkins Univ., Baltimore, MD; [7]Pediatrics and Neonatalogy, Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Background: We need new therapeutic targets for neonatal HI. SARM1, sterile alpha and TIR motif containing 1, the central executioner of axonal degeneration, is triggered by mitochondrial failure but its role in neonatal HI is unknown. SARM1's metabolomic signature is an increase in nicotinamide mononucleotide (NMN) to nicotinamide adenine dinucleotide (NAD+) ratio with catastrophically low NAD+ and elevated Cyclic ADP-ribose(cADPr) levels.
Hypothesis: In neonatal HI, SARM1 gene deletion provides neuroprotection and HI activates SARM1.
Methods: B6.a129X1-Sarm1tm1Aidi/J (SARM1 deficient) mice (n=10), and wildtype (WT) C57BI6 mice (n=6) were subjected to Rice-Vannucci model of HI on P10 (FiO2= 8% for 20 mins). Shams, n=6/genotype, were anesthesia exposed. P17 mice were perfusion fixed and brains sectioned for area measurements with Image J. Metabolites, from snap frozen ipsilateral and contralateral brain hemispheres (n=6) C57BL6, sham and HI mice, were measured with LC/MS. Results were compared with ANOVA and post hoc tests as appropriate.
Results: Group differences occurred in hippocampal, cortical, fimbria and corpus callosum areas with ipsilateral hippocampus, cortex and fimbria areas reduced in WT HI. No differences were observed in SARM1-/- HI vs sham or in SARM1-/- HI vs WT HI (Figure 1 a-h). Among 103 metabolites tested, group differences occurred in NMN, NAD+, NMN/NAD+ ratio and cADPr. cADPr was higher in ipsilateral HI vs contralateral and naïve brain (Figure1 i-l).
Conclusion: Given cADPr is the immediate product of SARM1 activation, our metabolomic results are intriguing though not conclusive for SARM1 activation. Neuropathology results dictate larger group sizes to determine if there is SARM1 neuroprotection. Given our previous work showing prolonged degeneration in the fimbria after neonatal HI, later time points are required to define effect of SARM1 on axonal neuroprotection. Though preliminary, further work to determine if SARM1 inhibitors in development can be therapeutic in neonatal HI is warranted.



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Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.15/B142

Topic: C.08. Ischemia

Support: NICHD Grant HD074593
NINDS Grant NS123814
2023 AAP Marshall Klaus Neonatal-Perinatal Research Award

Title: Cholinergic basal forebrain neuron rescue and cognitive recovery after neonatal hypoxic-ischemia by pharmacologically targeting the p75 neurotrophin receptor

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Abstract: Background: Child survivors of hypoxic-ischemic encephalopathy have memory and executive function deficits despite therapeutic hypothermia. These complex brain functions are tuned by forebrain cholinergic system efferents that are damaged after neonatal hypoxic-ischemia (HI). The survival of cholinergic basal forebrain (cBF) neurons is modulated by their expression of p75 neurotrophin receptor (p75NTR). p75NTR is thus a therapeutic target of damaged cBF neurons. LM11A-31 is an orally bioavailable and brain penetrant small molecule p75NTR ligand with neuroprotective effects in mouse models of adult acute stroke and neurodegenerative diseases. LM11A-31 is in clinical trials for Alzheimer's disease.
Aim: To determine if LM11A-31, as a late treatment, rescues cBF neurons and improves memory and executive function in survivors of neonatal HI.Methods: Brain damage was induced in C57BL6 mice using a modified Rice-Vannucci HI model at postanatal day 10 (P10). Littermates were exposed to anesthesia and served as Shams. LM11A-31 (vehicle, sterile water) or vehicle (veh) was administered intranasally (IN) (50 mg/kg/day, 5 days/week) to Sham and HI mouse pups from P14-P60. Mice were sacrificed at P270 after completion of touchscreen behavioral testing. Immunohistochemistry for choline acetyltransferase (ChAT) was done to determine if LM11A-31 treatment prevents cBF neuron degeneration after HI.
Results: LM11A-31 decreased the loss of ChAT neurons with HI in sublenticular regions at P270; HI veh had fewer neurons than HI drug ($p= 0.0414$, n=6 HI veh, 6 HI drug, 7 Sham) and Sham ($p=0.0194$). There was no difference between HI drug and Sham. HI veh also had less ChAT neurons than Shams ($p=0.011$) in nucleus basalis of Meynert (NBM), but neuron numbers in HI drug and Sham were not different. LM11A-31 embellished ChAT neuron dendrites in NBM. Mean dendrite length and area in HI veh was decreased compared to HI drug ($p=0.0409$) and Sham ($p=0.0376$). LM11A-31 also attenuated the effect of HI in Visual Discrimination (VD) and Reversal Learning (RL) testing with HI veh group needing more sessions to pass compared

to Sham in VD (p=0.0008) and RL (p=0.0007) whereas there was no difference between HI drug and Sham.
Conclusion: Late LM11A-31 treatment is therapeutic in neonatal mice with HI brain damage. It preserved cholinergic neuron cell body number in NBM and sublenticular regions of the cBF, protected dendrites in the NBM, and improved long-term brain function.

Disclosures: N. Kuter: None. **A. Cavanagh:** None. **B. Sollinger:** None. **O. Hatcher:** None. **V. Turnbill:** None. **S. Coleman:** None. **L.L. Jantzie:** None. **R. Chavez-Valdez:** None. **P. Kratimenos:** None. **L.J. Martin:** None. **F.J. Northington:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.16/C1

Topic: C.08. Ischemia

Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil)
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-Brazil)
Pró-Reitoria de Pesquisa (PROPESQ/UFRGS-Brazil)
Fundo de Incentivo à Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre (FIPE/HCPA-Brazil)

Title: Lactate prevents sensorimotor and cognitive impairment following neonatal hypoxia-ischemia

Authors: *I. TASSINARI, J. ZANG, N. RIBEIRO, J. MIOTTO TAUFFER, B. MARTINS, R. RIBEIRO NUNES, C. A. NETTO, A. PAZ, L. S. DE FRAGA;
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Abstract: The potential benefits of lactate (LAC) for the brain are gaining attention, particularly for neurological disorders. Neonatal hypoxia-ischemia (HI) is a leading cause of neurological disabilities in newborns. Moreover, LAC has been shown to be neuroprotective in cerebral ischemia models. Here, we evaluated the long-term effects of neonatal LAC administration following HI. Seven-day-old (P7) male and female Wistar rats (n=6-12) underwent surgery for right common carotid artery ligation followed by exposure to a hypoxic atmosphere (8% of oxygen) for 60 min at 37ºC. Animals were assigned to four experimental groups: HI (rats submitted to HI), HILac (rats submitted to HI that received LAC), SHAM (rats underwent fictitious surgery) and SHAMLac (SHAM rats that received LAC). LAC was administered intraperitoneally after HI twice. Sensorimotor function was assessed through the cylinder test (CT) and modified neurological severity score (mNSS), while cognitive decline was evaluated through novel object recognition (NOR). At P60, animals were euthanized to quantify brain

lesion volume (LV) by Nissl-stain. CT, NOR, and LV were analyzed by two-way ANOVA followed by Sidak for multiple comparisons and mNSS rating by Kruskall-Wallis followed by Dunn. In CT, HI animals showed a reduction in contralateral forepaw use (%) and an increase in the score reached in mNSS. On the other hand, sensorimotor impairments were reduced in juvenile male and female rats from HILac group ($p<0.05$). Adult HI animals from both sexes presented a reduction in the recognition index in NOR along with an increase in VL, which were also reverted by LAC ($p<0.05$). These results suggest neonatal LAC administration presents long-term benefits, improving cognitive impairment, sensorimotor deficits, and LV caused by HI. More experiments are required to unravel long-lasting LAC mechanisms after HI. This study was approved by the Institutional Animal Care and Use Committee (HCPA #21-0586) and supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-Brazil), Pró-Reitoria de Pesquisa (PROPESQ/UFRGS-Brazil), and Fundo de Incentivo à Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre (FIPE/HCPA-Brazil).

Disclosures: I. Tassinari: None. **J. Zang:** None. **N. Ribeiro:** None. **J. Miotto Tauffer:** None. **B. Martins:** None. **R. Ribeiro Nunes:** None. **C.A. Netto:** None. **A. Paz:** None. **L.S. De Fraga:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.17/Web Only

Topic: C.08. Ischemia

Support: PS1
COFECYT 2024

Title: Neuroprotective Effects of Raloxifene in an Oxygen-Glucose Deprivation/Reoxygenation Astrocyte Cell Model: Implications for Perinatal Asphyxia

Authors: N. TORO-URREGO[1], J. LUACES[2], T. KOBIEC[2], S. BORDET[3], M. D'AMBROSIO ANDRADE[2], C. ERRANDONEA[2], ***F. CAPANI**[4,5,6], S. MURGIAN[7];
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Abstract: Perinatal asphyxia causes hypoxic-ischemic brain injury and is an important risk factor for neurodevelopmental damage. The following decrease in tissue blood flow and oxygen concentration results in insufficient nutrient supply to the brain, energy depletion, increased free radical generation, and inflammation. In different pathological scenarios, selective estrogen receptor modulators (SERMs) exert several neuroprotective effects. In this study evaluate

Raloxifene as a neuroprotective agent in vitro. T98G cells were seeded in a DMEM culture medium containing 10% FBS and incubated for 2-3 days. Then cells were incubated in 1% O_2 in a hypoxia incubator for 9 hours. Then, reperfusion was performed with high-glucose DMEM supplemented with 10% FBS in 95% O_2/5% CO_2 (OGD/R). For drug treatments, cell cultures were incubated with 10 and 100 nM Raloxifene. Mitochondrial mass and membrane potential and reactive oxygen species were determined using Nonyl acridine orange (NAO), Tetramethyl Rhodamine Methyl Ester (TMRM), Dihydroethidium (DHE) and 2',7'-Dichlorofluorescein Diacetate (DCFDA) respectively, by flow cytometry and fluorescence intensity. Fluorescence images were acquired using a NIKON - Eclipse Ti-E PFS microscope, and cellular fluorescence was analyzed with Fiji. 50 cells were randomly selected on each microphotograph to determine the mean fluorescence value using the measure algorithm and selecting each cell manually via ROIs (Regions of Interest) management. Results. Morphological changes as smaller cell bodies and fewer cellular processes were observed following OGD compared with control cells. Raloxifene preserved cell morphology even in OGD/R cells. OGD/R exposure reduced cell viability. Raloxifene 100 nM and 10 nM improved cell survival — 65.3% and 70.6% — respectively compared to the control cell groups. Mitochondrial membrane potential was preserved by 58.9% 10 nM raloxifene and 81.57% 100 nM raloxifene cotreatment. Raloxifene co-treatment reduced superoxide production by 72.7% and peroxide production by 57.0%. Raloxifene improved cell survival and mitochondrial membrane potential, and reduced lipid peroxidation and reactive oxygen species (ROS) production, suggesting a direct effect on mitochondria. In conclusion, these findings suggest astrocytes may participate in the protective effects of raloxifene in hypoxic-ischemic brain injury.

Disclosures: N. Toro-Urrego: None. **J. Luaces:** None. **T. Kobiec:** None. **S. Bordet:** None. **M. D'Ambrosio Andrade:** None. **C. Errandonea:** None. **F. Capani:** None. **S. Murgian:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.18/C2

Topic: C.09. Stroke

Title: Impact of Perinatal Stroke on Motor and Cognitive Functions in a Mouse Model

Authors: *G. CUBONI[1], E. BERETTA[1], C. A. CAMPUZANO[2], L. VIGNOZZI[1], D. PINZAUTI[3], M. ALLEGRA[4,5,6], G. DEIDDA[1,4];
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Abstract: Adult cerebral ischemia (stroke) is a neurological injury caused by the occlusion of cerebral blood vessels and it is one of the leading causes of long-term disability. Notably, an ischemic stroke can occur also during brain development with the early perinatal period being

characterized by critical period windows when experience provides essential information for the proper maturation of sensory, motor, and cognitive functions. Despite the large amount of evidence on adult stroke, very little it is still known about the impact of a stroke occurring during perinatal ages in the developing brain. To address this question, we performed the middle cerebral artery occlusion (MCAO, a mouse model of ischemic injury) at perinatal age (P14) in mice pups and investigated the impact on motor and cognitive outcomes employing behavioral tests (gridwalk test, rotarod test, grip strength test, Y-maze test) longitudinally at different days (D) after stroke induction till adulthood. Overall, we did not find any general motor impairment assessed using the rotarod and grip strength tests. The gridwalk test revealed motor deficits at D2, and D9 in stroke mice in comparison to sham (control) mice. To investigate the impact on cognition we used the Y-maze test to assess working memory and the forced Y-maze to assess spatial novelty. Stroke mice showed spatial novelty memory motor deficits at D37. Histological analysis revealed that the volume of the brain lesion is on average 3 mm^3 at D79. Our findings revealed that perinatal stroke impacts on motor and cognitive functions later in life.

Disclosures: G. Cuboni: None. **E. Beretta:** None. **L. Vignozzi:** None. **M. Allegra:** None. **G. Deidda:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.19/C3

Topic: C.08. Ischemia

Support: Boettcher Webb-Waring Biomedical Research Grant

Title: Exploring AMPAkines in Pediatric Brain Recovery: Harnessing BDNF Signaling to Restore Synaptic and Cognitive Function Following Juvenile Global Cerebral Ischemia

Authors: J. E. HENRY[1], A. A. FINEBERG[1], T. B. MCVEY[1], E. TIEMEIER[1], J. E. ORFILA[2], P. S. HERSON[2], *R. M. DIETZ[3];
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Abstract: Children who suffer global cerebral ischemia (GCI) often have neurological damage that impacts learning and memory throughout childhood. Following juvenile global cerebral ischemia (GCI), long-term potentiation and memory are impaired for several weeks followed by some degree of recovery, indicating age specific plasticity which may provide opportunities for therapeutic interventions. AMPAkines are positive allosteric modulators of glutamatergic AMPA receptors. Some AMPAkines increase expression of brain-derived neurotrophic factor (BDNF), a molecule critical to the development of neuronal networks of learning and memory. This study aimed to investigate the use of AMPAkines as a therapeutic intervention to reverse synaptic dysfunction after GCI through their effects on the BDNF cascade. We hypothesize that delayed

administration of AMPAkine following GCI activates BDNF signaling and restores impaired hippocampal synaptic and cognitive function. Juvenile mice (PND 20-25) were subjected to 8-minute cardiac arrest and resuscitated. Fourteen days after resuscitation, AMPAkine LY404187 (1mg/kg) or vehicle was administered to mice. LTP was measured in acute hippocampal CA1 slices following theta-burst stimulation (40 pulses 100Hz). Contextual fear conditioning (CFC) was performed to evaluate hippocampal-dependent learning and memory. BDNF expression in hippocampal tissue was measured using ELISA. Western blots of BDNF-treated slices investigated the downstream effects of the BDNF pathway. Data presented as mean±SD. One-way ANOVA utilized unless otherwise stated. Administration of LY404187 14 days after GCI increased BDNF levels in sham and GCI mice (sham/vehicle:11245±864 pg/g, sham/AMPA: 16541±1018 pg/g, n=4, p=0.0003; GCI/vehicle: 4935±623 pg/g; GCI/AMPA: 14508±1985 pg/g, n=4, p<0.0001). Vehicle-treated slices revealed impaired LTP 14 days after GCI but ex vivo exposure to LY404187 (25μM) resulted in recovery of LTP in paired experiments (sham:155±13%; GCI/vehicle:112±12%; GCI/LY404187:156±13%, n=4, p=0.01). Intravenous administration of LY404187 13 days post-surgery recovered freezing behavior in GCI mice (GCI/vehicle: 20±3%, n=5; GCI/AMPA: 53±13%, n=6, p=0.001). Western blot revealed an increased ratio of phosphorylated protein kinase B (AKT) to total AKT in sham and GCI hippocampal tissue treated with BDNF (n=4, p=0.034; unpaired t-test). These results indicate delayed administration of AMPAkine after jGCI can recover hippocampal memory and learning through a BDNF/AKT dependent pathway.

Disclosures: J.E. Henry: None. **A.A. Fineberg:** None. **T.B. McVey:** None. **E. Tiemeier:** None. **J.E. Orfila:** None. **P.S. Herson:** None. **R.M. Dietz:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.20/C4

Topic: C.08. Ischemia

Support: 1R21NS128784

Title: Delayed fluoxetine administration restores hippocampal function in a juvenile global cerebral ischemia mouse model in a sex specific manner

Authors: *A. FINEBERG[1], J. HENRY[1], T. MCVEY[1], E. TIEMEIER[1], J. E. ORFILA[2], R. DIETZ[1];
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Abstract: Global Cerebral Ischemia (GCI) occurring during critical childhood developmental years often leads to learning and memory impairments due to significant neurologic dysfunction that negatively affect education through childhood. Published data from our lab has

demonstrated that juvenile mice models of GCI impair memory and synaptic function in a brain derived neurotrophic factor (BDNF) dependent pathway. BDNF is a key modulator of neuronal differentiation and growth, synapse formation and plasticity, and higher cognitive functions such as learning and memory. The aim of this study is to investigate the use of Fluoxetine (Flx), a drug that has been found to increase levels of BDNF, to recover memory and learning. We hypothesize that administration of Flx at delayed time points after global cerebral ischemia will result in improved functional outcome, including recovery of memory and learning behaviors. Male and female juvenile mice were subjected to an eight-minute cardiac arrest and resuscitation. Ten days post-surgery, Flx (10mg/kg) or vehicle was injected over a four-day period. Electrophysiology was performed to analyze long term potentiation (LTP), a marker for recovery of neuronal damage in hippocampal cells. Statistical analysis included ANOVA and significance was set at $p<0.05$.Male and female mice treated with vehicle revealed impaired LTP 14 days after GCI. Male mice treated with Flx showed recovery of LTP 14 days after GCI in paired experiments (sham:186.5±31; GCI/vehicle:114±22; GCI/Flx:163±35, n=6, p=0.03, ANOVA), while female mice treated with Flx did not show recovery of LTP 14 days after GCI in paired experiments (sham:143±19; GCI/vehicle:117±21; GCI/Flx:117±31, n=6, p=>0.99, ANOVA). The ELISA revealed no differences in BDNF levels between GCI and sham mice nor between male and female mice. These data indicate administration of Flx ten days post GCI over a four-day period recovers LTP in males, implying improvement of learning and synaptic function in the hippocampus in males but not females. Currently there are no accepted pharmaceutical treatments for recovery of learning and memory impairments in children with brain injury during their critical childhood developmental years. Investigation of Flx as an approach to restore hippocampal function following GCI may provide new avenues to study and broaden the therapeutic window for patients.

Disclosures: A. Fineberg: None. **J. Henry:** None. **T. McVey:** None. **E. Tiemeier:** None. **J.E. Orfila:** None. **R. Dietz:** None.

Poster

PSTR109: Perinatal Ischemia and Hypoxia

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.21/

Topic: C.10. Brain Injury and Trauma

Support: NIH R01

Title: Deciphering mechanisms of perinatal white matter injury-induced neuropsychiatric outcomes

Authors: J. JO, ***H. LEE**;
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Abstract: Perinatal white matter injury (pWMI) is the most common form of infantile brain injury associated with prematurity, maternal immune activation (MIA), and neonatal hypoxic-ischemic encephalopathy. Although neonatal death and chronic neurological morbidities such as cerebral palsy and intellectual disability are well-studied as sequelae of pWMI, there is mounting evidence that pWMI may result in neuropsychiatric disorders, including attention deficit hyperactivity disorder, autism spectrum disorder, anxiety, depression, and schizophrenia. However, the mechanisms by which pWMI contributes to neuropsychiatric disorders remain poorly understood. To underpin pathophysiological mechanisms leading to neuropsychiatric outcomes in pWMI patients, we generated a mouse model induced by a combination of 1) MIA leading to fetal inflammation and 2) early postnatal hypoxia to simulate pathological conditions in humans. By performing a battery of behavioral assays, we found that mice under pWMI exhibit deficits in cognitive function, impaired social interaction, and depression. Importantly, these behavioral alterations were more noticeable in male mice than female counterparts, suggesting sex-specific mechanisms may exist. In vivo DTI neuroimaging revealed abnormality of white matter integrity in multiple brain regions of pWMI-treated mice, correlating recent clinical studies that deformity in white matter is apparent in a wide range of neuropsychiatric disorders patients. In order to assess changes triggered by pWMI at the cellular level, we conducted single nuclei RNA sequencing and found significant modification in oligodendrocytes and excitatory neuronal populations by cell composition analysis and differentially expressed gene analysis. The decrease in mature oligodendrocytes and delayed myelination were further confirmed by histological analysis. Because myelination is imperative for brain circuit refinement and subsequent behavior, we examined changes in neuronal activity and found a brain region-specifically diminished c-fos activity. Electrophysiological evaluation of neuronal activity also revealed impaired synaptic transmission by pWMI. Collectively, we successfully established the model of pWMI-induced neuropsychiatric disease, and our results highlight the significance of white matter health and function for neuropsychiatric disease pathogenesis. Unraveling the interaction between oligodendrocytes and neurons and pinpointing crucial players through deeper analysis of DEGs will elucidate the mechanisms through which pWMI contributes to neuropsychiatric disorders.

Disclosures: J. Jo: None. **H. Lee:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.01/C5

Topic: C.10. Brain Injury and Trauma

Title: The Role of Rubicon in Traumatic Brain Injury Mouse Model

Authors: *S. THAPA[1], A. MEHRABANI-TABARI[2], O. PETTYJOHN-ROBIN[3], C. SARKAR[4], M. M. LIPINSKI[5];
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Abstract: Neuroinflammation induced by traumatic brain injury (TBI) serves as one of the primary instigators of secondary brain damage. These neuroinflammatory responses stem from neural cell death followed by the activation of resident cells and infiltration of peripheral immune cells. We have recently shown that macroautophagy (autophagy), a lysosome-dependent cellular catabolic pathway, plays a key role in the downregulation of neuroinflammation after TBI. Our data demonstrated that Becn1, a member of the Type III phosphatidyl inositol 3 kinase (PI3K) and an essential mediator of autophagy, is fundamental for regulation of inflammation by autophagy. Rubicon, a Rab7 effector protein, interacts with BECN1 to on one hand negatively regulate autophagy by competitively disrupting the Becn1-PI3K activity necessary for autophagosome-lysosome fusion, and on the other hand to promote non-canonical autophagy related pathway termed LC3-assocaited phagocytosis (LAP). The role of Rubicon remains largely unexplored after brain injury. To this end, we investigated how Rubicon modulates inflammatory responses and neurological functional outcomes following TBI in a mouse model. Our RNA-Seq data revealed that Rubcn-deficient mice display lower inflammatory responses 3 days post TBI. These responses were accompanied by downregulation of lipid metabolism in Rubcn KO mice. Consistently, qPCR results corroborate less inflammation in Rubcn-deficient mice in the acute phase of injury (Day 1 and 3). These alterations in inflammatory responses subsided by 29 dpi. However, we observed that Rubicon deficiency improves recovery in motor coordination following TBI. These findings suggest that therapeutically targeting Rubicon may provide neuroprotective approach to improving TBI outcomes.

Disclosures: S. Thapa: None. **A. Mehrabani-Tabari:** None. **O. Pettyjohn-Robin:** None. **C. Sarkar:** None. **M.M. Lipinski:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.02/C6

Topic: C.10. Brain Injury and Trauma

Support: NRF of Korea Grant 2022R1A2C1013084
NRF of Korea Grant 2018R1A6A1A03025221

Title: Desensitized 5-HT1A receptor causes the ME/CFS-like pathophysiology

Authors: *J.-S. LEE;
Daejeon Univ., Daejeon, Korea, Republic of

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a significant medical challenge, with no indisputable pathophysiological mechanism identified to date. Based

on clinical clues, we hypothesized that 5-hydroxytryptamine (5-HT) hyperactivation is implicated in the pathogenic causes of ME/CFS and the associated symptoms. We experimentally evaluated this hypothesis in a series of mouse models. High-dose selective serotonin reuptake inhibitor (SSRI) treatment induced intra- and extracellular serotonin spillover in the dorsal raphe nuclei of mice. This condition resulted in severe fatigue (rota-rod, fatigue rotating wheel and home-cage activity tests) and ME/CFS-associated symptoms (nest building, plantar and open field test), along with dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis response to exercise challenge. These ME/CFS-like features induced by excess serotonin were additionally verified using both a 5-HT synthesis inhibitor and viral vector for Htr1a (5-HT1A receptor) gene knockdown. Our findings support the involvement of 5-HTergic hyperactivity in the pathophysiology of ME/CFS. This ME/CFS-mimicking animal model would be useful for understanding ME/CFS biology and its therapeutic approaches.

Disclosures: J. Lee: None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.03/C7

Topic: C.10. Brain Injury and Trauma

Support: DOD Grant VR220084

Title: Cellular and electrophysiological changes in the adult murine retina associated with PNU-282987 eye drop treatment following blast exposure

Authors: *J. SPITSBERGEN[1], C. L. LINN[2];
[1]Western Michigan Univ., Kalamazoo, MI; [2]Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: Ocular trauma following blast injuries can result in vision loss via the death of retinal neurons. At least 9% of ocular injuries in US military veterans are associated with blast trauma. PNU-282987 is an alpha-7 nicotinic acetylcholine receptor agonist that has been shown to induce neurogenesis in both healthy and diseased adult mammalian retinas following eyedrop application. The objective of this research is to evaluate the structural and electrophysiological integrity of the retina following ocular blast trauma and eyedrop treatment with PNU-282987. The hypothesis to be tested in this study is that immediate and continuous eye drop application of PNU-282987 following ocular blast trauma causes morphological and functional changes in the mammalian retina. Ocular blast injury was induced in adult transgenic mice expressing TdTomato Muller glia (3-6 months old; both sexes) via a single 35 psi blast to the left eye delivered from a modified paintball gun. Animals were treated daily with a PBS eyedrop solution containing 1mM PNU-282987/1% DMSO post-blast for 4 weeks. Blast exposure at 35 PSI caused a significant loss of cells in all retinal layers (between 11 and 32% compared to un-blasted eye) after 4 weeks. Treatment with PNU-282987 resulted in significant recovery of cell

counts that were similar to control eyes. Immunohistochemical analysis demonstrated double labeled TdTom positive photoreceptors (15.26% +/- 4.3) and TdTom positive retinal ganglion cells (8.75% +/- 1.2) were present in blast exposed mice that were treated with PNU-282987 for 4 weeks. Retrograde labeling, using NeuroVue dye, indicates that axons from Muller glia derived retinal ganglion cells extend into the optic nerve. Electroretinogram (ERG) recordings were taken from control animals, from blast damaged animals and from animals exposed to blast followed by 4 weeks of PNU-282987 treatment. These recordings demonstrate a significant decrease in the amplitudes of the a-wave (50.51% +/- 8.9), b-wave (32.22% +/- 10), oscillatory potentials (OPs) 1 (35.63% +/- 10.6), 2 (30.62% +/- 5.5) and 3 (33.10% +/- 7.1), the photopic negative response (PhNR) (54.2 +/- 11.2), and flicker frequency recordings from 5 (31.56% +/- 12.1), 10 (48.11% +/- 10.2) and 20 Hz (35.57% +/- 8.5) following blast exposure. Treatment with PNU-282987 for 4 weeks following blast exposure was associated with a significant recovery of amplitude compared to blast responses (35-55%) in all aspects of the ERG recordings listed above ($n=6$, $p<.05$). These are the first experiments designed to address PNU-282987 induced recovery of functional changes in the retina after blast exposure.

Disclosures: J. Spitsbergen: None. **C.L. Linn:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.04/C8

Topic: C.10. Brain Injury and Trauma

Support: U.S. Department of Veterans Affairs
Department of Defense CDMRP ERP
Virginia Commonwealth University

Title: Altered dentate spike and hippocampal network dynamics in a lateral fluid percussion injury model of traumatic brain injury and post-traumatic epilepsy

Authors: *A. GIBSON[1,2], M. DEXHEIMER[1], D. J. KRUSIENSKI[1], P. KOCH[2];
[1]Virginia Commonwealth Univ., Richmond, VA; [2]Virginia Commonwealth Sch. of Med., Richmond, VA

Abstract: Epilepsy is one of the most common neurological diseases globally, it is increasing in rate, and carries one of the highest disease burdens of all neurological disorders in the United States. Post-traumatic epilepsy (PTE), a significant long-term complication of moderate-to-severe traumatic brain injuries (TBI), comprises as much as 20% of all structural epilepsies and commonly involves the temporal lobe. However, there are currently no effective early biomarkers or therapies to prevent the development of chronic seizures in high risk individuals, in part because the changes in the injured brain which lead to PTE are unknown. To better characterize the mechanisms underlying epileptogenesis following TBI, we interrogated the

hippocampal (HC) network at progressive time points after lateral Fluid Percussion Injury (FPI), a gold-standard model of PTE, using high channel count silicon probes and cortical EEG recordings in both anesthetized and awake, freely behaving adult male Sprague Dawley rats. In a preliminary cohort of animals (n= 9), 4 underwent FPI and 3 underwent a sham procedure. 1 sham and 2 FPI animals underwent acute recording 7 days after injury, as well as 2 naive animals at the same time point; 2 sham and 2 FPI animals underwent acute recordings 4 weeks after injury. In healthy rodents, bilaterally synchronized events in the dentate gyrus of the hippocampus called dentate spikes (DS) comprise one of the highest magnitude LFP events naturally occurring in the brain. We show that the bilateral synchronization of DS events markedly deteriorates after FPI, leading to interhemispheric changes to both the rate and amplitude of DSs, as well as alterations to the gamma oscillations which are associated with a DS. Theta-gamma coupling is known to be an important regulator of the dual internal HC and external EC input control over CA1 firing during spatial memory formation, and it has previously been shown that HC theta power is reduced after FPI. It has been shown that DSs promote spatial memory, and together these network disruptions may ultimately contribute to the cognitive deficits following TBI. We also find progressive hyperexcitability and synchronization of the HC surrounding DSs, evolving over time post-injury, and potentially contributing to the spontaneous late seizures which are the hallmark of PTE.

Disclosures: A. Gibson: None. **M. Dexheimer:** None. **D.J. Krusienski:** None. **P. Koch:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.05/C9

Topic: C.10. Brain Injury and Trauma

Support: I01Bx005708
IK6BX004Z14

Title: Aging modulates response to human adipose stem cell derived exosomes following traumatic brain injury

Authors: *S. S. ABDELMABOUD[1], N. A. PATEL[2], S. STEVENS, Jr.[3], C. LOGAN[4], P. C. BICKFORD[5];
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Abstract: Traumatic brain injury (TBI) is a leading cause of neurological complications including chronic memory deficits, dementia, and tau pathology. It is well known that aging is the primary risk factor for neurodegenerative diseases. Older TBI patients are at a higher risk for cognitive and motor decline after TBI exposure than younger individuals. The aim of the current

study is to explore how aging interacts to worsen prognosis in older TBI patients and to develop targeted strategies for this vulnerable population.Exosomes are a critical part of the human adipose stem cells secretome, containing cargo that limits the secondary cell death following TBI. Recently, our lab has shown efficacy of exosomes through intranasal (IN) delivery at 48 h post TBI in young mice. We aim to find the most effective dose in older TBI mice and characterize how exosomes interact with innate immunity.We conducted dose response experiments using controlled cortical impact (CCI) mouse model, at 8 days post CCI. Young and aged mice treated with IN exosomes at three different doses. We moved forward with dose 20µg and extended the timeline to 30 days post CCI. We evaluated motor and cognitive function and performed IHC. We stained for neuroinflammation markers including microglia, and astrocytes. As well as neurogenesis marker. For further investigation, we have isolated microglia and astrocytes for proteomic processing to explore the molecular changes following exosomes treatment.The results showed that exosomes significantly reduced motor and cognitive dysfunction in an age dependent manner. TBI mice treated with exosomes showed significant decrease in neuroinflammation markers near the lesion site in cortex and hippocampus. The bioinformatic prediction of proteomic profiling of microglia showed a significant regulation of neuroinflammation pathways and significant downregulation of proinflammatory regulators and cytokines for aged group at 30 days post CCI.From that we concluded that exosomes enhanced the recovery following TBI in aged mice. In addition, a major action of exosomes is to modulate the secondary immune response to injury by interacting with the innate immunity mainly Microglia and astrocytes. Furthermore, exosomes showed significant enhancement of neurogenesis in aged TBI mice.In this study we aim to understand how different ages impact response to exosomes treatment post TBI and to move this promising therapy forward and develop it for clinical practice.

Disclosures: S.S. Abdelmaboud: None. **N.A. Patel:** None. **S. Stevens:** None. **C. Logan:** None. **P.C. Bickford:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.06/C10

Topic: C.10. Brain Injury and Trauma

Support: George M. Leader Foundation
Neurosurgery Department

Title: A Common Mutation in the Homeostatic Iron Regulator Gene Leads to Modifications in Behavior and Recovery Following Traumatic Brain Injury

Authors: *M. NOLT, E. NEELY, R. JIN, G. LI, J. R. CONNOR;
Penn State Col. of Med., Hershey, PA

Abstract: Iron is required to sustain a healthy central nervous system (CNS). Iron aides in enzymatic reactions, myelinogenesis, neurotransmitter synthesis, and oxygen transport. Due to iron's high prevalence in the CNS, it can become dysregulated in several disease states such as neurotrauma. In the case of traumatic brain injury (TBI), iron becomes abundant due to cell membranes rupturing, microhemorrhages, and larger subdural and epidural hemorrhages. The excess of iron present in the brain parenchyma can overwhelm innate antioxidant systems leading to persistent and increased brain damage beyond the site of TBI impact. In this study, we wanted to investigate how a genetic model of subclinical iron overload (*HFE H63D*) would impact recovery from TBI. Previous data from our lab indicated the antioxidant mechanisms present in *HFE H63D* are upregulated. This is potentially due to persistent innate subclinical iron overload which primes the antioxidant systems. From this data, we *hypothesize* innate subclinical iron overload present in *HFE H63D* generates an environment that promotes healing post-TBI. To test this hypothesis, we conducted a study utilizing controlled cortical impact (CCI) TBI model. We used *HFE H67D* (mouse homolog) and *WT HFE* males and female that were randomly selected to each surgery group (CCI TBI or sham TBI). After a 21-day recovery period, the mice were split into immunohistochemical (IHC) or western blot analysis groups. Behavioral analysis was also performed to assess recovery. Half of the mice underwent Barnes maze and novel object memory testing while the other half were assessed on rotarod motor behavioral testing. The behavior results indicated *HFE H67D* males and females spent less time immobile, had reduced primary and total latency on Barnes maze, and spent more time investigating the novel object. However, both genotypes performed equally on rotarod motor assessment. Overall, the *behavioral data indicated* *HFE H67D* mice have reduced memory impairment and anxiety-like behaviors post-TBI indicating better outcomes. The histological data is not yet complete, but *pilot study data* from our lab showed increased GFAP presence in the *HFE H67D* ipsilateral hippocampus post-TBI. These data highlight a potential mechanism of increased astrocytic healing post-TBI leading to decreased memory impairment. The results from this study show subclinical iron overload may have neuroprotective effects post-TBI potentially through a primed antioxidant mechanism.

Disclosures: M. Nolt: None. **E. Neely:** None. **R. Jin:** None. **G. Li:** None. **J.R. Connor:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.07/C11

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant RO1EY028039
NIH Grant R01NS114397

Title: Collateral sprouting as a mechanism of CNS repair: is there a role for Wallerian degeneration?

Authors: *A. S. ALEXANDRIS[1], J. YI[2,1], C. LIU[2,1], J. BELAMARICH[1], A. PENG[1], V. E. KOLIATSOS[3];
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Abstract: Although neuronal regeneration in the CNS is limited, the extraordinary capacity of the CNS for repair has been demonstrated in classical examples of functional recovery after injury in animal models and in humans. Collateral sprouting, a form of compensatory branching of surviving axons, may allow the formation of new connections and the restoration of circuits and, thus, constitute a potentially important target for therapeutic interventions. Traumatic axonal injury (TAI) is the most common neuropathology in traumatic brain injury (TBI) and causes significant morbidity due to disconnection of neural networks. In TAI, the axonal segments located distal to the injury site consistently degenerate due to Wallerian degeneration (WD), a highly conserved molecular program of axon-self-destruction, whose significance in the CNS is not clear. Here we utilize a mouse model of diffuse TAI (Impact acceleration TBI) in order to explore for the first time the time-course of collateral plasticity in the visual pathway and the role of WD in CNS repair. Two-month-old C57BL/6J mice were transduced intravitreally for genetic labeling of RGC axons and synapses or injected with anterograde or transsynaptic tracers for labeling of terminals and/or postsynaptic neurons. Functional connectivity was assessed by post-synaptic cFos expression after light stimulation and visual evoked potentials (VEP). Our experiments show that TBI results in 40-50% loss of axons and retinocollicular terminals at 7 days which is reflected by deficits in VEPs and post-synaptic cFos expression. In wt mice this is followed by restoration of terminals to nearly baseline levels by 14 days post-injury and for the duration of the study (2mo). In contrast, while inhibition of WD in SARM1 KO mice does not impede the eventual restoration of retinocollicular terminals, it is associated with significant delay in collateral sprouting. These findings indicate that, in the adult mouse CNS, a portion of visual circuitry can restore its connectivity after injury by homotopic/homologous sprouting of surviving neurons. As in the PNS, Wallerian degeneration may facilitate regeneration by clearance of disconnected axons. Further elucidation of this process and related mechanisms will be very important for the design and optimization of therapeutic interventions such that to promote axonal maintenance without suppressing innate repair processes.

Disclosures: A.S. Alexandris: None. **J. Yi:** None. **C. Liu:** None. **J. Belamarich:** None. **A. Peng:** None. **V.E. Koliatsos:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.08/C12

Topic: C.10. Brain Injury and Trauma

Support: CCCRP Grant CO210066

Title: Characterization of a Traumatic Brain Injury and Organophosphate Exposure Polytrauma Mouse Model Using Multiple Behavioral, Physiological, and Histopathological Methods.

Authors: *J. JANSSEN, J. LEIGHTON, M. ELLIS, A. METHVIN, E. A. JOHNSON;
Med. Toxicology, USAMRICD, Gunpowder, MD

Abstract: Treatment strategies are well established for traumatic brain injury (TBI) and organophosphate (OP) compound exposures alone. However, the resulting synergistic effects of a TBI/OP polytrauma and the effectiveness of standard medical countermeasures (MCM) for both injury modalities in the polytrauma model are unknown. Understanding progressive central nervous system (CNS) injury dynamics are essential to improve care, particularly in cases of brain injuries, as it allows for a detailed examination of cellular changes and helps inform further treatment strategies. Thus, this study measured quantitative behavioral, EEG, and physiological observation (injury metrics) with a focus on the inflammatory responses, neuronal degeneration, and blood-brain barrier (BBB) integrity for each individual injury and the combined TBI/OP polytrauma. To investigate these aims, we used a novel TBI/OP polytrauma mouse model using human acetylcholinesterase knock-in/serum carboxylesterase knockout (C57BL/6-Ces1ctm1.1LocAChEtm1.1Loc/ J; KIKO) mice. For each experiment, mice received an open craniectomy for controlled cortical impact TBI and a subcutaneous wireless transponder for electroencephalographic (EEG) monitoring. Then, mice either received a TBI, were exposed to OP, or were given a TBI/OP polytrauma along with all standard MCM. Mice were monitored for 72 hours post-exposure and injury metrics were quantified prior to euthanasia and brain extraction. Using immunohistochemistry, paraffin-embedded slides were labeled with glial cell markers to gauge the inflammatory response to individual and TBI/OP polytrauma injury. Across all exposures, an inflammatory response was evident, although the intensity of this response varied depending on injury type and severity. The integrity and permeability of the BBB were also assessed with differences seen among the injury modalities. Finally, degenerating neurons were labeled to visualize and quantify the extent of neuronal damage with differences again observed among the different injury groups. In sum, neuropathology and the inflammatory response to the TBI/OP polytrauma were in agreement with other metrics showing more deficits and poorer outcomes compared to individual injuries.

Disclosures: J. Janssen: None. **J. Leighton:** None. **M. Ellis:** None. **A. Methvin:** None. **E.A. Johnson:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.09/C13

Topic: C.10. Brain Injury and Trauma

Title: Combining laminar local field potentials and independent component analysis to quantify changes in hippocampal microcircuitry following traumatic brain injury

Authors: *M. DEXHEIMER[1], A. GIBSON[1], V. C. PATEL[2], D. J. KRUSIENSKI[1], P. KOCH[2]; [1]Virginia Commonwealth Univ., Richmond, VA; [2]Neurosurg., Virginia Commonwealth Sch. of Med., Richmond, VA

Abstract: Epilepsy occurs as a result of moderate to severe traumatic brain injury (TBI) in 10-20% of cases. Some risk factors for post traumatic epilepsy (PTE) are known, but the mechanisms by which PTE arises are not. Loss of mossy cells and interneurons within the dentate gyrus (DG) has been implicated in the development of hippocampal (HC) seizures, including after TBI, potentially via increased hyperexcitability within the microcircuitry of the HC as a consequence of lost inhibitory control over entorhinal afferent inputs. Here, we use a fluid percussion injury model (FPI) of PTE in rats and laminar high channel count silicon probes to interrogate the microcircuitry of the HC through extracellular recordings. We aim to characterize changes in the post-synaptic response to entorhinal input within the DG as well as its downstream influence on CA1. One challenge of electrophysiological interpretation arises when the normal architecture of the HC is altered due to pathological changes such as TBI. In order to address this, we generate current source density (CSD) representations of recorded local field potentials (LFPs) in conjunction with independent component analysis (ICA). It has been established that ICA can be used to effectively separate LFPs in the hippocampus into pathway specific independent activities. These resulting independent components describe the inputs of multiple distinct presynaptic populations. Additionally, constraints identified using a priori spatial information from our laminar probes can be applied to ICA to further refine the separation of source activity. These methodologies allow us to define and classify patterns of post synaptic activity in the DG and CA1 sub-region that, in conjunction with anatomical localization of our probe, reveal the distinct combinations of entorhinal inputs contributing to these post-synaptic patterns. In a preliminary cohort of animals, 3 underwent FPI and 2 underwent sham injury. Sham injured and 2 FPI underwent acute recordings 4 days post injury and 1 FPI underwent acute recordings 4 weeks post injury. Our ICA based approach identified clear inputs into the molecular layer of the dentate in both sham and injured. When extracting LFP width and amplitude characteristics as well as averaging CSD representations of ICA detected events, our preliminary results show examples of post-injury morphological changes in post-synaptic electrographic events (“dentate spikes”) in the DG. This may reflect pathological alterations in the patterns of entorhinal inputs to the HC. This work demonstrates a use of ICA to improve interpretability of CSD representations via event detection when altered parameters are unknown.

Disclosures: M. Dexheimer: None. **A. Gibson:** None. **V.C. Patel:** None. **D.J. Krusienski:** None. **P. Koch:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.10/C14

Topic: C.10. Brain Injury and Trauma

Support: VA Grant (1I01BX006062-01A1)

Title: Ascorbate promotes post-TBI neuroprotection by enhancing DNA hydroxymethylation

Authors: *P. JOSHI[1,2], C. KOZHIKKADAN DAVIS[1], A. CHOKKALLA[1], R. VEMUGANTI[1,2,3];
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Abstract: Every year, ~69 million people worldwide sustain some form of Traumatic brain injury (TBI), which depending on the magnitude of impact and the degree of damage, results in motor, cognitive and neuropsychiatric dysfunction. Oxidative stress that occurs during the acute phase of injury is a major proponent of the secondary brain damage and functional loss associated with TBI. Ascorbate (Vitamin C) is a potent antioxidant that also acts as a cofactor to the Ten-eleven Translocation (TET) family of proteins which catalyze the oxidation of the epigenetic modification 5mC to 5hmC. As 5hmC is known to enhance transcription of protective genes and promote neuronal survival under adverse conditions, we tested the efficacy of ascorbate after a mild to moderate grade controlled cortical impact injury in adult male C57BL/6 mice. Cohorts of mice were injected with different doses of ascorbate (*i.p.*; 250 mg/Kg or 500 mg/Kg or 750 mg/Kg) or saline at 5 min, 24h and 48h after TBI. Ascorbate treated cohort showed significantly reduced lesion volume and improved motor function recovery (estimated by rotarod test and beam walk test) at 3 and 5 days after TBI compared with saline treated cohort (n =10/group). Ascorbate treated mice also showed significantly increased TET activity (estimated colorimetrically) and higher 5hmC levels (analyzed by dot blot) in the perilesional cerebral cortex compared with the saline cohort. Thus, our studies show that ascorbate treatment can modulate the levels of the 5hmC epigenetic modification through increased TET activity and can result in enhanced neuroprotection after TBI.

Disclosures: P. Joshi: None. **C. Kozhikkadan Davis:** None. **A. Chokkalla:** None. **R. Vemuganti:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.11/C15

Topic: C.10. Brain Injury and Trauma

Title: Low-intensity Pulsed Ultrasound Improved Cognitive Function After Experimental Traumatic Brain Injury: Regulating the Activation of A1/A2 Reactive Astrocyte

Authors: *N. HSIAU[1], W.-S. SU[2], S.-F. CHEN[3], F.-Y. YANG[4];
[1]Dept. of Biomed. Imaging and Radiological Sci., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]Grad. Inst. of Toxicology, Natl. Taiwan Univ., Taipei, Taiwan; [3]Physical Med. and

Rehabil., Cheng Hsin Gen. Hosp., Taipei, Taiwan; [4]Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Objectives Long-lasting cognitive and motor deficits after traumatic brain injury (TBI) are associated with an increased risk of neurodegenerative disease including dementia and Parkinson's disease. Currently, all phase III clinical trials in neuroprotection have failed to show improvement in outcome for TBI patients. Therefore, there is an unmet need to develop an effective treatment for TBI. Low-intensity pulsed ultrasound (LIPUS) has been recently demonstrated to be a non-invasive physical modality in treating brain neurodegenerative diseases by reducing neuroinflammation and inducing the secretion of brain-derived neurotrophic factor (BDNF). The aim of this study was to investigate the effects of LIPUS on cognitive recovery and astrocyte-mediated neuronal damage following mouse TBI.
Methods In this study, controlled cortical impact model was used to establish TBI model in C57BL/6 male mice; LIPUS was treated 5 min after TBI, once per day up to 14 days; and TNA2 astrocyte and N2A neuron cell lines were also used. For experimental analysis, spatial learning and memory were assessed by Y-maze test and Morris water maze test (MWM); injury volumes were measured by MRI image and Cresyl violet; signaling pathways were examined by western blots; and inflammatory responses were verified by ELISA kits.
Findings Firstly, LIPUS improved the spatial memory retention ability in experimental TBI mice by improving the performance in training trial of MWM without swimming speed changed between groups. The protective effects provided by LIPUS after TBI may come from improving the neuron damages and neurogenesis in mice. Also, reduction of tissue damages and brain edema were contributed by attenuating neuron death. Collectively, tissue loss, neuronal death, and synaptic function in TBI were significantly improved after LIPUS treatment. Neuroinflammation is thought to be associated with cognitive impairment, including activation and infiltration of glia cells. The study then found that LIPUS improved the distribution changes of astrocytes and microglia cells, reduced pro-inflammatory cytokines expression, and enhanced anti-inflammatory cytokines and neurotrophic factors expression after TBI. Moreover, LIPUS reduced the activation of neurotoxic and proinlammatory A1 reactive TNA2 astrocyte to prevent N2A neuron death.
Conclusions In summary, LIPUS stimulation can improve the cognitive function, increase the survival of neuronal cells and neurogenesis, and reduce the infiltration of inflammatory cells. This study provides a promising new treatment method to solve the problem of long-term neurological deficits in TBI patients.

Disclosures: N. Hsiau: None. **W. Su:** None. **S. Chen:** None. **F. Yang:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.12/C16

Topic: C.10. Brain Injury and Trauma

Title: The role of neuregulin in exercise induced neuroprotection: a study of mouse model of brain injury

Authors: *J. SHARMA, A. ANAND;
P.G.I.M.E.R, Chandigarh, India

Abstract: The role of neuregulin in exercise induced neuroprotection: a study of mouse model of brain injury Jyotsna Sharma[1], Akshay Anand[2]1.*Neuroscience Research Lab, Department of Neurology, PGIMER, Chandigarh, India*2.*Neuroscience Research Lab, Department of Neurology, PGIMER, Chandigarh, India*
Background: Exercise has been shown to have positive impact on brain health and may even have a neuroprotective function as it has been demonstrated to increase the synthesis of neurotrophic factors, support neuronal survival, and improve neuroplasticity. Similarly, the formation, maintenance, and repair of the central and peripheral nervous systems are aided by neuregulin, a neuroprotective molecule. The link between exercise and neuregulin in mediating neuroprotection has been the subject of increased research to better understand the processes behind this association and its possible applications to the prevention of neurodegenerative disorders.**Keywords:** Exercise, Neuregulin, Neuroprotection**Aim-**; To investigate the role of neuregulin mediated neuroprotective effects of exercise on learning and memory.Methodology; This study will be conducted at three stages. (1) Exercise will be provided to mouse after that mouse model of memory loss will be created. (2) Exercise will be provided to young mouse and serum will be transplanted to the older mouse. (3) At this stage 60 runner participant will be recruited and neuropsychological and cognitive assessment will be done using various test. After this ELSA will be performed for various neuroprotective molecule. Plasma will be isolated from runners and transplanted to mice model of memory loss. To analyze the effect of exercise on expression of Neuregulin and its receptor various neurobehavioral and molecular test will be performed at each stage.**Hypothesis:** Exercise plays a neuroprotective role by enhancing the expression of Neuregulin and its receptor in mouse model.*Conflict of Interest:* No conflict of interest
Corresponding Author: Akshay Anand, Ph.D.ProfessorNeuroscience Research LabDepartment of Neurology, PGIMER, Chandigarh, India.

Disclosures: J. Sharma: None. **A. Anand:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.13/C17

Topic: C.10. Brain Injury and Trauma

Support: 5P20GM109098-08

Title: Hypoperfusion exacerbates traumatic brain injury outcomes

Authors: *Z. M. WEIL[1], B. WHITEHEAD[2], D. R. CORBIN[3], N. ZHANG[3], J. R. BUMGARNER[3], K. KARELINA[2];
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Abstract: Mild-moderate traumatic brain injuries (TBIs) are prevalent, and while many individuals recover, there's evidence that a significant number experience long-term health impacts, including increased vulnerability to neurodegenerative diseases. These effects are influenced by other risk factors, such as cardiovascular disease. Our study tested the hypothesis that a pre-injury reduction in cerebral blood flow (CBF), mimicking cardiovascular disease, worsens TBI recovery. We induced bilateral carotid artery stenosis (BCAS) and a mild-moderate closed-head TBI in male and female mice, either alone or in combination, and analyzed CBF, spatial learning, memory, axonal damage, and gene expression. Findings showed that BCAS and TBI independently caused a ~10% decrease in CBF. Mice subjected to both BCAS and TBI experienced more significant CBF reductions, notably affecting spatial learning and memory, particularly in males. Additionally, male mice showed increased axonal damage with both BCAS and TBI compared to either condition alone. Females exhibited spatial memory deficits due to BCAS, but these were not worsened by subsequent TBI. Gene expression analysis in male mice highlighted that TBI and BCAS individually altered neuronal and glial profiles. However, the combination of BCAS and TBI resulted in markedly different transcriptional patterns. Our results suggest that mild cerebrovascular impairments, serving as a stand-in for preexisting cardiovascular conditions, can significantly worsen TBI outcomes in males. This highlights the potential for mild comorbidities to modify TBI outcomes and increase the risk of secondary diseases.

Disclosures: Z.M. Weil: None. **B. Whitehead:** None. **D.R. Corbin:** None. **N. Zhang:** None. **J.R. Bumgarner:** None. **K. Karelina:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.14/C18

Topic: C.10. Brain Injury and Trauma

Support: Merit Review Grant I01BX004837
Merit Review Grant I01BX005750

Title: Endothelium-targeted deletion of microRNA-15a/16-1 promotes neuropathological and functional recovery in experimental traumatic brain injury

Authors: *S. LI[1,3], N. QIU[1,3], C. ZHOU[1], T. XIONG[1], X. HUANG[1], J. XUE[1,3], C. DIXON[2,3], J. CHEN[1,3], K. YIN[1,3];
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Abstract: Traumatic brain injury (TBI) is a common experience among veterans and is associated with sensorimotor and cognitive decline and an increased risk of other neurodegenerative diseases. MicroRNAs (miRs) have been implicated in multiple central nervous system (CNS) diseases. Dysregulated plasma miR-15a/16-1 levels have been found in TBI individuals. However, the role of miR-15a/16-1 in neurotrauma is poorly explored. To investigate the essential role and underlying mechanisms of endothelial miR-15a/16-1 in regulating long-term neurological outcomes and recovery after TBI. Experimental TBI was induced in vascular endothelial cell-selective miR-15a/16-1 conditional knockout (EC-miR-15a/16-1 cKO) mice and wild-type littermate controls by unilateral controlled cortical impact (CCI) (3.5-3.7 m/sec, 1.5 mm depth, 3 mm tip diameter, 150 ms dwell time). The neurobehavioral tests (cognitive and sensorimotor deficits), white matter injury, and neuronal loss were then evaluated and quantitatively analyzed for five weeks. Brain leakage of Alexa Fluor 555-conjugated cadaverine and IgG, as well as the infiltration of peripheral macrophages and neutrophils were evaluated to examine the blood-brain barrier (BBB) integrity. FACS-sorted vascular endothelial cells from TBI mouse brains and sham controls were carried out for RNA-seq and bioinformatic analysis. Five weeks post CCI, mice developed remarkable sensorimotor and cognitive impairments, myelin loss and axonal damage in corpus callosum and external capsule, and neuronal loss in cerebral cortex and hippocampal CA1 region. Compared to WT controls, endothelium-targeted deletion of miR-15a/16-1 significantly reduced CCI-induced neuronal loss, demyelination, and axonal injury, and improved long-term neurobehavioral outcomes in TBI mice. Genetic deletion of miR-15a/16-1 in endothelium also led to less BBB leakage, reduced infiltration of peripheral macrophages and neutrophils, and diminished activation of astrocytic activation in mouse brains 1-3 days after CCI. Mechanistically, RNA-seq results showed that the differential expression genes were found in FACS-sorting ECs from EC-miR-15a/16-1 cKO mouse brains to be associated with the activation of multiple anti-neuroinflammatory and vascular biological processes. Endothelial miR-15a/16-1 negatively regulates neuronal loss, white matter damage, and long-term neurological recovery following TBI via aggravating BBB damage and neurovascular inflammation. Cerebrovascular endothelium specific-targeted inhibition of miR-15a/16-1 activity may serve as an effective therapeutic approach for restorative treatment in brain trauma.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.15/C19

Topic: C.10. Brain Injury and Trauma

Support: DFG grant, #457586042

Title: Characterization of microthrombi-mediated blood-brain-barrier dysfunction following traumatic brain injury

Authors: *A. C. WEHN[1,2], M. SCHIFFERER[3], B. GROSCHUP[4], J. SHROUDER[4], N. A. TERPOLILLI[5], N. PLESNILA[2,6], I. KHALIN[2,7];
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Abstract: Background: Traumatic brain injury (TBI) manifests with reduced cerebral blood flow and heightened blood-brain-barrier (BBB) permeability, yet the underlying mechanisms remain elusive. This study explores the involvement of microvascular occlusions (mVOs) in the traumatic penumbra and their contribution to these processes. Aim: To characterize mVO composition in an experimental TBI model and explore their influence on BBB permeability. Method: mVOs were visualized in C57BL/6 mice by systemic administration of super-bright 30 nm lipidic nanodroplets (LnDs) one hour following controlled cortical impact (CCI). Brains were investigated by fluorescent confocal imaging. Additionally, caveolin (Cav1) knockout mice (Cav1tm1Mls/J) and wildtype controls (WT) were used to investigate the mechanisms of BBB opening at the site of mVOs. Results: Our findings demonstrate that 50% of mVOs correlated with the extravasation of albumin, fibrinogen, IgG, and LnDs within the traumatic penumbra. Immunohistochemistry revealed mVO components comprising erythrocytes, platelets, fibrin, and leukocytes, indicative of microthrombosis. The extravasation of blood-borne molecules positively correlated with cellular presence within mVOs (n=426 clots; $R=0.31$, $p=0.02$) and inversely with fibrin content ($R=-0.64$, $p<0.001$). Genetic deletion of Cav1 notably reduced LnD extravasation across the BBB compared to WT controls (n=5 animals per group, $p=0.002$). Conclusions: Our study shows the occurrence of microthrombosis in the traumatic penumbra, amplifying BBB permeability at mVO sites. Additionally, the caveolin transport system seems to be a prominent mediator in BBB opening. These insights propose a novel theranostic avenue targeting the traumatic penumbra, offering potential diagnostic and therapeutic interventions for traumatic brain injury.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.16/C20

Topic: C.10. Brain Injury and Trauma

Support: P20 GM109098

Title: Mechanisms of long-term microemboli formation following traumatic brain injury

Authors: *M. BARBOUR[1], D. R. CORBIN[1], N. ZHANG[1], K. KARELINA[2], Z. M. WEIL[3]; [1]West Virginia Univ., Morgantown, WV; [2]Neurosci., West Virginia Univ., Morgantown, WV; [3]Neurosci., West Virginia Univ. - PhD in Neurosci., Morgantown, WV

Abstract: Each year, 2.5 million Americans seek treatment for traumatic brain injury (TBI), which can be caused by a bump, blow, or jolt to the head. Yet even after symptoms resolve, epidemiological data show that TBI increases vulnerability to both ischemic and hemorrhagic strokes, which are a leading cause of disability and death. Even after mild injuries, this vulnerability lasts for months to years. The mechanisms leading to persistent risk of both ischemic and hemorrhagic strokes after TBI are not well understood. Previous work in our lab has identified increased blood brain barrier permeability and intravascular immunoglobulin and fibrin(ogen) up to 28 days after TBI in mice. We hypothesized that TBI causes 1.) long-term formation of small emboli through hemodynamic changes and accumulation of serum proteins in the vascular lumen and 2.) blood brain barrier dysfunction that drives hemorrhagic transformation. After inducing a moderate closed-head TBI or sham injury, we systemically injected 4µm fluorescent microspheres at both 72- and 1-hour prior to euthanasia. Two colors of spheres allowed us to differentiate between microspheres injected at different timepoints. Here we present data generated in mice showing decreased washout of intravascular fluorescent microspheres at both seven and 28 days after moderate TBI compared to sham-injured animals. Future directions include identifying which cells or coagulation components are implicated in this process and the mechanisms driving hemorrhagic transformation. Determining the mechanisms responsible for long-term TBI-induced vascular dysfunction and how this dysfunction causes ischemic and hemorrhagic strokes, can improve clinical treatment and patient outcomes for TBI and strokes.

Disclosures: M. Barbour: None. **D.R. Corbin:** None. **N. Zhang:** None. **K. Karelina:** None. **Z.M. Weil:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.17/C21

Topic: C.10. Brain Injury and Trauma

Support: W81XWH1810166
W81XWH1810167

W81WXH2210461
W81XWH2210462
HT9425-23-1-0296

Title: Posthemorrhagic Hydrocephalus Induces Multifaceted Injury in CSF Dynamics Detectable in Both the Brain and the Eyes

Authors: *H. HELMBRECHT[1], J. ROBINAUGH[2], R. PATEL[2], V. O. OMONIYI[3], T. L. BELECKY-ADAMS[4], S. ROBINSON[5], L. L. JANTZIE[6];
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Abstract: Acquired hydrocephalus, or elevated intracranial pressure from abnormal cerebrospinal fluid (CSF) accumulation, commonly occurs in adults after intraventricular hemorrhage (IVH) and subarachnoid hemorrhage. Posthemorrhagic hydrocephalus (PHH) can be life-threatening, often accompanying sepsis and requiring surgical shunt insertion to divert CSF. Inflammation, blood, and cell-free hemoglobin activate cytotoxic and oxidative pathways limiting spontaneous recovery of CSF dynamics and contributing to chronic brain injury. We hypothesized that systemic and cerebral inflammation exacerbates PHH by chronically altering the CNS microenvironment. We predicted simultaneous, self-propagating damage to the choroid plexus, ependyma and glymphatic system detectable by multimodal ultrastructural, microstructural and functional brain and eye imaging. To model PHH, we combined inflammation with IVH: we injected lipopolysaccharide systemically at postnatal day 21 (P21) and P23 and litter-matched lysed red blood cells into each lateral ventricle at P25. We performed MRI, histology, and ependymal analysis with equal rat numbers from both sexes at P45 (young adult: $n \geq 6$ per group) and P60 (adult: $n \geq 7$ per group). We performed diffusion tensor imaging and structural T1 and T2 imaging of the ventricular system, optic nerve, and optic disc concomitant with glymphatic tracing using Dotarem contrast. With MRI, we compared PHHP rats to controls finding (1) enlarged ventricles, enlarged subarachnoid space around the optic nerve, and papilledema ($p<0.05$), (2) reduced glymphatic clearance of Dotarem tracer, and (3) reduced fractional anisotropy and microstructural injury in major white and gray matter structures. Ependymal cilia were evaluated in ultrastructural and functional domains using scanning electron microscopy and live cell assays (fluorescent bead tracking with Imaris), respectively. Motile cilia from PHH animals were denuded and flattened; diffuse ependymal loss was detected. Compared to controls, cilia from PHH animals displayed uncoordinated movement, beat inefficiently, and moved beads across the ependymal surface slowly ($p<0.05$). In conclusion, PHH induces multifaceted injury across CSF-containing spaces detectable in the brain and eyes. This injury is typified by ventriculomegaly, enlarged subarachnoid space around the optic nerve, papilledema, ependymal cell loss, and impairments in cilia and glymphatic function. Together, these data support propagating inflammation as a critical component of PHH and CSF dynamics. Multimodal brain and eye imaging may prove useful in diagnostic and therapeutic response biomarker discovery.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.18/C22

Topic: C.10. Brain Injury and Trauma

Support: Department of Defense #PR221805

Title: The effects of post hemorrhagic hydrocephalus on rat optic disc and retina

Authors: *T. BELECKY-ADAMS[1], H. HELMBRECHT[2], L. L. JANTZIE[3];
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Abstract: Hydrocephalus is characterized by an abnormal accumulation of cerebrospinal fluid in the brain, resulting in increases in intracranial pressure. While often associated with children, hydrocephalus is also prominent in aging patients and those suffering from hemorrhage and/or brain injury. Papilledema, a swelling of the optic disc resulting from an increase in intracranial pressure, is a hallmark feature of hydrocephalus. Patients with papilledema include an increase in the fluid in the subarachnoid space surrounding the optic nerve, a reduction in retinal venous outflow, axoplasmic stasis in retinal ganglion cells (RGCs), and a loss of RGCs. The described studies have investigated the effects of hydrocephalus in adult rats with post-hemorrhagic hydrocephalus (PHH) on the optic nerve, optic disc, and retina. A rat model of PHH was created by intraventricular injection of lysed red blood cells collected from littermates at P25 preceded by priming injections of lipopolysaccharide. T2 weighted high-resolution MRI on brain and optic nerve was completed prior to the collection of opening pressures and tissue collection between P45 and P100. Measurements of the optic disc, vasculature and retinal layers were taken using NIH ImageJ of 12μm hematoxylin and eosin-stained sections and OCT. RGC number was determined by analyzing retinal flat mounts co-labeled with BRN3A and RBPMS. Results indicate an increased intracranial pressure in PHH rats in comparison to naïve rates using opening pressure. Optic disc and nerve MRIs of PHH revealed optic disc swelling and an increase in fluid surrounding the optic nerve in comparison to naïve. Both histological and OCT analyses showed a significant increase in the size of the optic disc in PHH rats in comparison to naïve controls at P60 and P100. There was a loss of cells co-labeled with RGC markers BRN3A and RBPMS within 300-550μm of the optic disc at P60 with an average number of 20.3 +/-3.4 RGCs (N=5) found in naïve rats in comparison to an average of 11.4 +/- 2.5 (N=6) in PHH rats. Finally, histological analysis on vasculature of the ganglion cell layer indicates an increase in the number of larger blood vessels in comparison to controls. In conclusion, changes investigated in hydrocephalic rats are consistent with changes found in patients with papilledema and warrant further investigation into the mechanisms of post-hemorrhagic papilledema.

Disclosures: T. Belecky-Adams: None. **H. Helmbrecht:** None. **L.L. Jantzie:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

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Topic: C.10. Brain Injury and Trauma

Support: W81XWH1810166
W81XWH1810167
W81XWH2210461
W81XWH2210462

Title: Multimodal MRI Imaging Shows Altered Cerebrospinal Fluid Dynamics in Preclinical Posthemorrhagic Hydrocephalus of Prematurity

Authors: *R. PATEL[1], H. HELMBRECHT[2], T. HECK[3], J. ROBINAUGH[4], K. BELDAY[4], S. ROBINSON[5], L. L. JANTZIE[1];
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Abstract: Posthemorrhagic hydrocephalus of prematurity (PHHP) often occurs in early preterm infants after a severe intraventricular hemorrhage (IVH) secondary to prenatal systemic inflammation such as chorioamnionitis (CAM). PHHP is marked by progressive ventriculomegaly, increased intracranial pressure, macrocephaly, and neurological deficits. A major cause of hydrocephalus after hemorrhage and persistent injury is abnormal cerebrospinal fluid (CSF) dynamics. We hypothesized that inflammation would persistently alter CSF dynamics, including glymphatic function. Our objective was to use multimodal MRI, including a T1 Flash-3D-weighted sequence with a gadolinium-based contrast agent, Dotarem, to analyze CSF dynamics in our previously established, clinically-relevant preclinical PHHP model. Durable PHHP was induced in rats with in utero exposure to CAM and bilateral intracerebroventricular injection of littermate lysed red blood cells (IVH) on postnatal day 1 (P1). Study groups were divided into PHHP (CAM+IVH; n=3), CAM only; (n=15), and control (n=9). Sexes were evenly distributed. MRI imaging was done using a 11.7T Bruker BioSpin scanner at >postnatal day 32. After T2 and DTI sequences, Dotarem was introduced into CSF via cisterna magna injection. After injection, a series of T1-Flash-3D scans was taken at 5-minute intervals for 3 hours. Using Imaris, mean intensity of regions of interest at each time point was quantified and normalized to the baseline. Rats with CAM and PHHP both had ventriculomegaly and changes in DTI, including alterations in fractional anisotropy, axial and radial diffusivity compared to sham ($p<0.05$). However, PHHP animals had increased intracranial pressure with marked ventricular expansion. Dotarem tracer uptake in both sham and CAM animals slowly increased over the 3-hour interval in subarachnoid spaces, ventricles, and prefrontal cortex. Over the 3-hour window, Dotarem uptake in the subarachnoid space of CAM rats was greater than in the shams. In contrast, in animals with PHHP the Dotarem signal immediately infused into the enlarged ventricles and remained for the duration of the scan while slowly increasing in the subarachnoid spaces and prefrontal cortex consistent with increased absorption and decreased

tracer clearance. We found altered CSF dynamics in the CAM and PHHP animals when compared to shams supporting the hypothesis that IVH in the setting of inflammation alters CSF flow and glymphatic clearance, initiating and contributing to persistent hydrocephalus. Future studies will explore the molecular mechanisms of altered CSF dynamics and the glymphatic system dysfunction to develop PHHP treatments.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.20/C25

Topic: C.10. Brain Injury and Trauma

Support: W81XWH1810166
W81XWH1810167
W81XWH2210461
W81XWH2210462

Title: Non-surgical therapy suppresses gliopathy and white matter injury after post-traumatic hydrocephalus

Authors: *V. O. OMONIYI[1], A. ODUKOYA[1], J. ROBINAUGH[1], X. JIA[1], B. VIJAYAKUMAR[1], R. PATEL[1], H. HELMBRECHT[1], S. ROBINSON[2,3], L. L. JANTZIE[1,4,5,3]; [1]Pediatrics, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Neurosurg., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; [4]Kennedy Krieger Institute, Baltimore, MD; [5]Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract: Post-traumatic hydrocephalus (PTH) is a serious complication of traumatic brain injury (TBI). Several weeks often occurs between the initial TBI and development of symptomatic hydrocephalus requiring shunt insertion. This interval between the TBI and PTH provides a window of opportunity for therapeutic intervention to prevent a permanent shunt. We discovered that inflammation impacts CSF dynamics and that PTH is amendable to neurorepair by immunomodulation. Specifically, we used a novel neuroreparative cocktail with roxadustat (ROX), a member of a new class of oral prolyl hydroxylase domain inhibitors plus high dose melatonin (MLT). We hypothesized that along with normalizing CSF dynamics in PTH, ROX+MLT would mitigate hallmarks of gliopathy and energy failure in the ventricular system and brain regions critical to cognitive function. To induce PTH secondary to systemic inflammation and TBI, young adult rats received 3 mg/kg LPS or saline control intraperitoneally on postnatal day 21 (P21) and P23. On P25, rats of both injury groups underwent TBI via impact. Shams received anesthesia and incision. Injured rats of both sexes were randomly allocated to a

10-day dosing regimen for ROX (10mg/kg)+MLT(20mg/kg) or saline vehicle from P26-P36. Differences were examined using two-way ANOVA with Bonferroni correction ($p<0.05$; n=8-10/group). Rats with PTH developed ventriculomegaly and elevated intracranial pressure at P45 consistent with PTH ($p<0.01$). PTH also induced a significant gliosis with changes in the morphology of microglia and astrocytes in striatum and ependyma. Specifically, PTH altered length of astrocytic processes, total area of astrocytic processes, branch processes, process terminal points and astrocyte complexity (all $p<0.05$). PTH also induced degradation of myelin in multiple cortical layers and subcortical white matter and caused profound microstructural injury compared to controls (all $p<0.05$). Treatment with ROX+MLT reversed this gliopathy and improved mitochondrial health in choroid plexus. Specifically, ROX+MLT normalized mitofusin2 mRNA expression and mitigated injury to white matter microstructure ($p<0.05$). In conclusion, PTH induces chronic gliopathy, white matter injury and mitochondrial failure. Together, these pathophysiological alterations may suppress neurological recovery. Neuroimmunomodulation with a cocktail after TBI may provide a clinically-viable therapeutic strategy to prevent PTH and improve neural repair.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.21/C26

Topic: C.10. Brain Injury and Trauma

Support: NIH/NINDS Grant 5R01NS126273-03
AHA Grant 23TPA1069224
AHA Grant 24SCEFIA1255866

Title: Activation of liver X receptor signalling mitigates myelin pathology following traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is a significant cause of death and disability in both military and civilian populations, impacting 1.5 million individuals in the U.S. TBI survivors often experience severe brain damage and loss of memory. Demyelination is a notable pathological consequence of traumatic brain injury (TBI), which has a devastating impact on brain function, memory, and cognition. Neuronal axons rely on myelin sheaths, which provide insulative protective coverings, facilitating the propagation of nerve impulses. Therefore, the major challenge of post-TBI care is to alleviate demyelination. As such, the liver X receptor

(LXR) is a nuclear receptor that plays a crucial role in lipid metabolism and cholesterol homeostasis. Previous studies indicated that enhanced LXR signaling can promote cholesterol levels in oligodendrocytes, the cells responsible for myelin formation in the central nervous system, to support oligodendrocyte maturation and remyelination. We thus hypothesize that treatment with GW3965, a synthetic agonist of LXR, to activate LXR signaling can alleviate demyelination and memory deficits following TBI. Method: C57BL/6 mice were subjected to a closed head injury (CHI) using a stereotaxic precise impactor (RWD Life Science, velocity 5.1 m/s, depth 1.00 mm, and dwell time 80 ms). GW3965 was administrated via oral gavage one day following TBI for two weeks (10 mg/kg/day). Following treatment, memory- and cognition-related behavioral tests (e.g., novel objection recognition test and Y-maze) were conducted. Myelin pathology was further assessed by immunofluorescence staining and capillary-based immunoassay. Results: Our results indicate that treatment with GW3965 significantly reduced TBI-induced demyelination via myelin basic protein, microtubule-associated protein 2, and axonal membrane protein (Caspr). Additionally, mice treated with GW3965 had better behavioral test performance following TBI compared to untreated animals. Our findings suggest that targeting LXR signaling is a potential therapeutic approach in treating TBI-induced myelin pathologies and associated cognitive impairments.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.22/Web Only

Topic: C.10. Brain Injury and Trauma

Support: NHMRC Grant APP187156

Title: Beyond Injury: Exploring the role of SARM1 in Cortical Axon Connectivity

Authors: *E. IZADI[1,2], B. BENNETT[3], A. KING[3], A. J. CANTY[3];
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Abstract: Axon degeneration is a hallmark of traumatic brain injury and neurodegenerative disease and is a significant contributor to global mortality and disability rates. Sterile Alpha and TIR motif-containing protein 1 (SARM1) is emerging as a key player in modulating axon degeneration. Following an injury, SARM1 is activated, which results in rapid depletion of NAD+ and energy stores in the axon, which accompanies signalling cascades that lead to axon degeneration. SARM1 activation appears to hasten axonal degeneration, but its role in maintaining axonal connectivity in the cerebral cortex both in the absence of injury and after an

injury is poorly understood. This study investigates the synaptic plasticity of excitatory axons in the adult sensory-motor cortex in the presence and absence of SARM1. We used cranial windows and live *in vivo* multiphoton imaging to directly visualise excitatory axons in the cortex of Thy1-GFP-M (on a C57BL6 background, WT-GFP, control group) crossed with SARM1 null mutants (SARM1KO-GFP, experimental group). We collected images of cortical axons at 48-hour intervals to compare axon morphology, synaptic density, and synaptic turnover in the presence and absence of SARM1 in adult male mice (3-12 months old, WT-GFP: 21 axons, 12 mice and SARM1KO-GFP: 21 axons, 9 mice). We identified long axonal segments (mean length 335 µm +/- 140µm) in the upper layers of the cortical neuropil that were rich in both *terminaux* and *en passant* synaptic boutons. We find that axon morphologies are similar in the presence and absence of SARM1 and, synaptic density and turnover (a measure of dynamic synapse elimination and formation) are also comparable. In a subset of axons that were discrete axonal endings (WT-GFP: 10 axons, 5 mice and SARM1KO-GFP: 10 axons, 7 mice), we used laser-mediated axotomy to remove the terminal segment of the axon and measured the synaptic response of the surviving axonal segment (still connected to the cell body). We find that synaptic density is maintained on the surviving axonal segment for at least 96 hours after the lesion in both genotypes, but synaptic turnover is differentially affected in the absence of SARM1. Our findings illustrate that *in vivo* time-lapse imaging facilitates a deeper understanding of the synaptic dynamics in absence of SARM1. This is a major milestone in understanding the role of SARM1 in synaptic plasticity in response to injury in the cortical axons, paving the way for the future investigation.

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Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

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Program #/Poster #: PSTR110.23/C27

Topic: C.10. Brain Injury and Trauma

Title: Failed negative geotaxis: measurement techniques and implications for neurodegeneration and traumatic brain injury

Authors: *J. M. VASU[1], K. D. VU[2], R. E. HARTMAN[2];
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Abstract: Failed Negative Geotaxis in Drosophila Melanogaster: Measurement Techniques and Implications for Traumatic Brain Injury and Alzheimer's Disease Authors J. Vasu[1], K. Vu[1], R. Hartman[1]**Affiliation Hartman Behavioral Neuroscience Lab, Loma Linda University, School of Behavioral Health[1], United States of AmericaAbstract***Drosophila Melanogaster***, the common fruit fly, is commonly used in behavioral neuroscience research. Negative Geotaxis is a natural inclination to climb, commonly observed in *Drosophila*

Melanogaster. While negative geotaxis has been extensively studied as models for aging, neurodegeneration, and drug effects, researchers have failed to observe errors in this behavior. There is currently no research on Failed Negative Geotaxis (FNG), when flies fail to exhibit their natural climbing behavior and fall. As the common factors that can contribute to locomotion deficits, investigating how FNG relates to age, sex, and climbing speed with a control group, traumatic brain injury (TBI) group, and Alzheimer's Disease (AD) group on a standardized RING assay provides a novel behavioral measurement without adaptation difficulties. We have developed a method for recording these errors, FNG, using a traditional Rapid Iterative Negative Geotaxis (RING) assay. FNG changes were significantly associated with sex, age, and climbing speed. Our study aims to introduce FNG as a new dimension in *Drosophila* behavior analysis, capturing a specified deviation from typical negative geotaxis. This research not only contributes novel mechanisms in assessing locomotion deficits, but does so with a common place behaivoral neuroscience assay. Investigation of FNG in relation to TBI and AD may provide novel understandings of these condition's symptoloogy in *drosophila melanogaster*.

Disclosures: J.M. Vasu: None. **K.D. Vu:** None. **R.E. Hartman:** None.

Poster

PSTR110: Brain Injury, Neuro-Behavioral Consequences, Interventions and Treatment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.24/C28

Topic: C.10. Brain Injury and Trauma

Support: National Key Research and Development Program of China (Grant No. 2021YFA1101802-2)
National Key Research and Development Program of China (Grant No. 2021YFA1101802-2)

Title: Npas4 loss exacerbates synaptic dysfunction and promotes cognitive impairment in mice after traumatic brain injury

Authors: *W. SHI[1], H. CHAO[1], J. JI[2], X. WANG[1], Q. HE[1], P. ZHAO[1], T. WANG[1], C. CHEN[1], N. CHEN[1], Y. YE[1], L. XU[1], J. HU[1], J. JI[1];
[1]the First Affiliated Hosp. of Nanjing Med. Univ., Nanjing, China; [2]China Pharmaceut. Univ. (CPU), Nanjing, China

Abstract: There are still not enough effective drugs or treatments for Traumatic brain injury (TBI). Therefore, we aim to find one or more new therapeutic targets that can help TBI patients with neurological repair and functional rehabilitation. In this study, we used single nuclear RNA sequencing(snRNA-seq) to perform a detailed analysis of human brain tissue samples (TBI group: n=19; Control group: n=4) for TBI and controlled cortical injury (CCI) mice model. Because of neurons are more vulnerable after TBI, we selected neurons for differential expression gene analysis. In both human and mice tissues, the expression of Npas4 after TBI

significantly increased in neurons, and was significantly different with the control group. Bulk RNA-sequencing also supported our conclusion.Then, the results of qRT-PCR, Western Blot and immunofluorescence experiments were consistent. In vitro, glutamate was used to simulate the excitotoxic effects after TBI. The fluorescence intensity of Synaptophysin1 and Postsynaptic density protein 95(PSD-95) demonstrated impaired synaptic function. The structure and function of synapses with Npas4 knockdown were worse. In vivo, pAAV-hSyn-EGFP-shRNA (Npas4) was injected to reduce Npas4. Golgi staining and behavioral experiments showed sh-Npas4+TBI group had less dendrite spine density and more severe cognitive impairment than sh-NC+TBI group. Next, CUT&Tag sequencing is to explore the downstream target genes of Npas4. Therefore, we conclude that Npas4 alleviates synaptic dysfunction and cognitive impairment after TBI, and it is expected to become a new and effective target for clinical treatment of TBI.

Disclosures: W. Shi: None. **H. Chao:** None. **J. Ji:** None. **X. Wang:** None. **Q. He:** None. **P. Zhao:** None. **T. Wang:** None. **C. Chen:** None. **N. Chen:** None. **Y. Ye:** None. **L. Xu:** None. **J. Hu:** None. **J. Ji:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.01/C29

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Utilizing Hebbian Plasticity to Enhance Respiratory Function in Individuals with Spinal Cord Injury: A Proof of Concept Study

Authors: *B. CHEN[1,2,3], M. A. PEREZ[1,2,4,3];
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Abstract: Individuals with high cervical spinal cord injury (SCI), particularly at the levels of C3-C5, often face respiratory challenges that significantly impact their quality of life and increase mortality risks. A primary factor contribute to these complications is diaphragm dysfunction. Hebbian stimulation, a noninvasive neurostimulation technique based on the principle of spike-timing dependent plasticity (STDP), has shown efficacy in promoting the recovery of both upper and lower limb muscles in humans with SCI. In this study, we explored the effects of Hebbian stimulation on the diaphragm muscle in individuals with chronic high cervical SCI. To induce Hebbian plasticity, corticospinal volleys generated by transcranial magnetic stimulation (TMS) over the diaphragm motor cortex were precisely timed to coincide with the arrival of antidromic potentials in motoneurons elicited by electrical stimulation of the phrenic nerve, with a timing interval of 1-2 ms. We evaluated motor evoked potentials (MEPs) in the diaphragm muscle before and after administering 180 paired-pulses of Hebbian stimulation.

Additionally, we assessed respiratory function before and after the Hebbian stimulation in individuals with SCI. Our findings revealed that MEP size at rest and electromyographic activity in the diaphragm during maximal inspiratory efforts increased after a single session of Hebbian stimulation in SCI participants. Furthermore, a ventilator-dependent participant underwent 40 sessions of Hebbian stimulation combined with standard physical therapy. Remarkably, we observed improvements in vital capacity, forced vital capacity, forced expiratory volume, and maximal voluntary ventilation after repeated sessions compared to baseline measures. Additionally, the ultrasound data showed enhancement in diaphragm contraction ratio after 40 sessions. These results suggest that STDP-like plasticity induced by Hebbian stimulation could serve as a promising approach to enhance respiratory function following high cervical SCI.

Disclosures: B. Chen: None. **M.A. Perez:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.02/C30

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant HD07418
NINDS Grant R35 NS122336
VA Grant I01RX003715
VA Grant I01RX002848

Title: Do elbow flexor and extensor muscles respond similarly to Hebbian stimulation in humans with spinal cord injury?

Authors: *C. L. P. BUTLER[1,2,3], M. A. PEREZ[1,4,3];
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Abstract: Individuals with cervical spinal cord injury (SCI) exhibit limited motor recovery in elbow extensors compared to elbow flexor muscles. The goal of our study was to assess the effect of Hebbian stimulation on corticospinal excitability in elbow flexor and extensor muscles in humans with and without spinal cord injury (SCI). During Hebbian stimulation, corticospinal volleys evoked by transcranial magnetic stimulation (TMS) were timed precisely to arrive at corticospinal-motoneuronal synapses of the biceps and triceps brachii muscles 1-2 ms prior to the arrival of antidromic potentials elicited through electrical stimulation of the musculocutaneous and radial nerves at the brachial plexus. The central conduction time (CCT) and peripheral conduction time (PCT) [calculated by using the latency of motor evoked potentials (MEPs), C-roots, and maximal motor responses], were similar between muscles in control and SCI participants. Thus, by using the appropriate interstimulus interval between TMS

and peripheral nerve stimulation, we were able to target both muscles concurrently using suprathreshold stimulation. TMS was delivered at 100% of the maximum stimulator output (MSO), above the resting motor threshold for both muscles in controls (biceps=59.8±13.0% of the MSO; triceps=70.5±19.5% of the MSO) and SCI (biceps=72.8±20.6% of the MSO; triceps=85.0±10.5% of the MSO) participants. We tested the effect of Hebbian stimulation on MEPs elicited by TMS over the arm representation of the motor cortex in biceps and triceps brachii before and after 180 paired pulses in humans with and without chronic cervical SCI. We found that MEP size increased after stimulation in the biceps brachii to a larger extent than in the triceps brachii in control (biceps=264.6±111.9% of baseline, triceps=178.1±72.5% of baseline) and SCI (biceps=396.7±273.3% of baseline, triceps=143.4±84.0% of baseline) participants. Our findings suggest that in humans, spike-timing dependent plasticity mechanisms are more easily engaged in elbow flexors compared to elbow extensors muscles. This knowledge might contribute to the design of targeted strategies aiming to enhance upper limb function after SCI.

Disclosures: C.L.P. Butler: None. **M.A. Perez:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.03/C31

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS
VA

Title: Spasticity is More Prevalent in Knee Extensor Compared with Knee Flexor Muscles in Humans with Chronic Spinal Cord Injury

Authors: *R. POWELL[1], S. SANGARI[1], M. A. PEREZ[2];
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Abstract: Although it is known that spasticity is present in lower limb muscles in humans with spinal cord injury (SCI), little is known about the distribution of spasticity between flexor and extensor muscles. To address this question, we measured spasticity in the quadriceps femoris and hamstring muscles in individuals with incomplete SCI exhibiting ambulatory capability using a clinical exam (Modified Ashworth Scale, MAS). Individuals with SCI were separated into non-spastic (MAS=0, 1) and spastic (MAS=2, 3, 4) groups. To understand the contribution of descending motor pathways to spasticity, we measured motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation, knee flexion and extension maximal voluntary contractions (MVCs) using electromyography (EMG) and torque, and the StartReact response (a shortening in reaction time evoked by an acoustic stimuli of 110 dB that engage the reticulospinal pathway) in SCI participants and in age-matched control subjects. We found that 60% of SCI participants

tested showed spasticity in the quadriceps muscle. None of the SCI participants showed spasticity in the hamstring muscles. Regardless of spasticity, SCI participants showed decreases in the magnitude of the MVCs measured by EMG and torque and in the maximal MEP in the quadriceps and hamstring muscles compared with controls. Moreover, the magnitude of these outcomes was always further reduced in the hamstring compared with the quadriceps muscle in controls and SCI participants. The StartReact response was larger in the quadriceps in participants with spasticity but like controls in the hamstring. These findings demonstrate an asymmetric presentation of spasticity in knee flexor and extensor muscles in people with SCI being more pronounced in knee extensor compared to flexor muscles. Our results also support previous findings showing that muscles with spasticity present reduced corticospinal and larger reticulospinal contributions.

Disclosures: R. Powell: None. **S. Sangari:** None. **M.A. Perez:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.04/C32

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS
VA

Title: Age Affects Differentially Transmission in Corticospinal and Reticulospinal Pathways in Humans with Spinal Cord Injury

Authors: *S. SANGARI[1], M. A. PEREZ[2];
[1]Shirley Ryan AbilityLab, Chicago, IL; [2]Ctr. for Neural plasticity, Arms & Hands, Shirley Ryan Abilitylab, Chicago, IL

Abstract: Spinal cord injury (SCI) occurs more frequently in older adults. Yet, the effect of age on transmission in the descending motor pathways remains largely unknown. To address this question, we used electrophysiological approaches to examine transmission in the corticospinal and reticulospinal pathway in younger (<50 years) and older (≥50 years) adults with and without incomplete SCI. We measured motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation, maximal voluntary contractions (MVCs), and the StartReact response (a shortening in reaction time evoked by an acoustic stimuli of 110 dB that engage the reticulospinal pathway) in the rectus femoris muscle. We found that the magnitude of the maximum MEP and MVCs were decreased in older compared with younger control participants. In contrast, the StartReact response was similar between older and younger control participants. Older adults with SCI showed further reduction in the magnitude of the maximum MEP size and MVCs, and larger StartReact response (a greater shortening in reaction time) compared to older and younger control subjects. These findings suggest that descending motor pathways are differentially

affected by age following SCI, with the corticospinal pathway being more affected compared with the reticulospinal pathway. This knowledge might contribute to inform the development of age-appropriate therapeutic interventions for people with SCI.

Disclosures: S. Sangari: None. **M.A. Perez:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.05/C33

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Modulation of forelimb cutaneous reflexes during locomotion following a cervical spinal cord injury in adult cats

Authors: *S. YASSINE, R. AL ARAB, J. AUDET, S. MARI, O. EDDAOUI, P. JEHANNIN, J. HARNIE, C. NADEAU, A. FRIGON;
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Abstract: During locomotion, afferents from the skin continuously inform the nervous system about the interactions of the body with its external environment. For instance, when the foot dorsum contacts an obstacle during the swing phase, cutaneous mechanoreceptors send signals to spinal circuits to elicit a whole-body response that alters the trajectory of the simulated limb while coordinating the other limbs. Spinal cord injury (SCI) disrupts the way our body responds to external perturbations, as shown in our recent studies where we characterized changes in cutaneous reflexes following incomplete thoracic SCIs (Mari et al. 2024a, b). However, changes in cutaneous reflexes following cervical SCI (cSCI) remain unexplored. Here, we stimulated the right superficial radial nerve and recorded cutaneous reflex responses in muscles of the four limbs during treadmill locomotion at 0.4 m/s in two cats, before and after a lateral cervical hemisection at C2-C3 on the right side. Preliminary data revealed changes in reflex response patterns after cSCI. In the intact state, homonymous short-latency excitatory responses (P1) in the right biceps brachii, triceps brachii, brachialis, and extensor carpi radialis longus were strongly phase-modulated. After cSCI, these responses remained but the depth of the phase modulation decreased. The amplitude of these homonymous responses increased at 6-7 weeks after SCI compared to the intact state before returning towards intact values at 16 weeks post-SCI. Responses and phase modulation in hindlimb muscles, such as the homolateral and diagonal soleus, as well as the diagonal sartorius were maintained after cSCI. However, in some hindlimb muscles, responses appeared after cSCI that were not present in the intact state. For instance, homolateral P1 and mid-latency excitatory (P2) responses appeared in the right biceps femoris posterior (RBFP), while mid-latency inhibitory (N2) responses appeared in the right vastus lateralis (RVL). While phase-dependent modulation of the N2 responses in RVL remained similar at the two timepoints after cSCI, the occurrence of the P1/P2 responses in RBFP was reduced at the late time point. Therefore, our preliminary results show a reorganization of

cutaneous reflex pathways from the right superficial radial nerve to the ipsilesional forelimb and hindlimbs after cSCI. The appearance of responses in some hindlimb muscles could help strengthen interlimb coordination.

Disclosures: S. Yassine: None. **R. Al Arab:** None. **J. Audet:** None. **S. Mari:** None. **O. Eddaoui:** None. **P. Jehannin:** None. **J. Harnie:** None. **C. Nadeau:** None. **A. Frigon:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.06/C34

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Recovery of quadrupedal and hindlimb-only locomotion after staggered lateral cervical and thoracic hemisections in adult cats

Authors: *J. AUDET, S. YASSINE, R. AL ARAB, C. LECOMTE, S. MARI, O. EDDAOUI, P. JEHANNIN, J. HARNIE, C. NADEAU, A. FRIGON;
Univ. de Sherbrooke, Sherbrooke, QC, Canada

Abstract: Hindlimb locomotor recovery in various mammals after complete thoracic spinal cord injury (SCI) is due to the presence of a lumbar central pattern generator (CPG) that interacts with sensory feedback from the hindlimbs. Studies have shown that the lumbar locomotor CPG also plays a prominent role following incomplete thoracic SCIs (Barrière et al. 2008, Audet et al. 2023). However, the involvement of the lumbar CPG in hindlimb locomotor recovery following incomplete cervical SCI remains unexplored. We collected kinematic and EMG data in six cats during quadrupedal treadmill locomotion from 0.4 to 1.0 m/s and in four cats during hindlimb-only treadmill locomotion (forelimbs placed on a stationary platform) from 0.1 to 0.6 m/s before (intact) and each week after a cervical lateral hemisection on the right side at C2-C3. We then performed a second lateral hemisection on the left side at T10-T11. 10-12 weeks after the second hemisection, we performed a complete spinal transection at T12-T13. All six cats recovered quadrupedal treadmill locomotion at 0.4 m/s without perineal stimulation after the first (5-11 weeks) and second (7-11 weeks) hemisections. All four cats recovered hindlimb-only locomotion from 0.1 to 0.6 m/s after the first (3-9 weeks) and second (1-8 weeks) hemisections without perineal stimulation. With perineal stimulation, hindlimb-only locomotion recovered more quickly after the first (2 weeks) and second (1-2 weeks) hemisections. At 1-2 days after spinal transection, none of the cats expressed hindlimb-only locomotion without perineal stimulation. With perineal stimulation, two of six cats performed weak alternating movements. One week after transection, two of six cats performed hindlimb-only locomotion without perineal stimulation. Two weeks after spinal transection, only one of these two cats maintained the ability to generate hindlimb-only locomotion. With perineal stimulation at 1-2 weeks after transection, one cat had a robust hindlimb locomotion pattern and two other cats showed weak locomotion. Three weeks after transection, none of the six cats performed hindlimb-only locomotion without

perineal stimulation. However, with perineal stimulation, all six cats could generate hindlimb locomotion, albeit with some deficits in paw placement bilaterally, particularly on the right side. Therefore, our results suggest that the recovery of hindlimb locomotion in the cervical-thoracic staggered hemisections paradigm depends on spared pathways from the cervical cord and/or from the brain and less on an intrinsic lumbar mechanism compared to single or staggered thoracic hemisections.

Disclosures: J. Audet: None. **S. Yassine:** None. **R. Al Arab:** None. **C. Lecomte:** None. **S. Mari:** None. **O. Eddaoui:** None. **P. Jehannin:** None. **J. Harnie:** None. **C. Nadeau:** None. **A. Frigon:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.07/C35

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canadian Institute of Health Research Project Grant (PJT 180556)

Title: Electrophysiological and optogenetic mapping of connectivity patterns and locomotor function of dI3 interneurons in the lumbar spinal cord

Authors: *S. NASIRI, A. M. LALIBERTE, T. V. BUI;
Biol., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Spinal locomotor networks use sensory feedback to adapt their activity to maintain stability in response to perturbations of the body. The important ability to adapt the activity of these spinal networks in response to changes in the body or external environment is mediated in part by a population of spinal interneurons, called dI3 neurons. These neurons receive cutaneous and proprioceptive inputs, and there is data supporting the idea that they provide some excitatory drive to spinal locomotor networks. However, the specific connectivity of dI3 neurons to spinal motor circuits throughout the extent of the spinal cord is not well known. Through optogenetic activation of these neurons and electrophysiological recordings, we mapped the functional connectivity of dI3s to different circuits throughout the lumbar spinal cord. We demonstrate that the activation of dI3 subpopulations activates, through monosynaptic or oligosynaptic connections, motoneurons throughout the lumbar cord in a bilateral manner. Furthermore, long trains of photoactivation of dI3 subpopulations is sufficient to recruit spinal locomotor networks. We suggest that from such extensive projection patterns of dI3 neurons throughout the lumbar spinal cord, dI3 subpopulations that integrate very specific source of sensory information are capable of influencing the activity of multiple muscles across the hindlimbs.

Disclosures: S. Nasiri: None. **A.M. Laliberte:** None. **T.V. Bui:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.08/C36

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Postdoctoral Fellowship Research Grant (890234)
Canadian Institute of Health Research Project Grant (PJT 180556)

Title: Examining the role of dI3 neurons in forelimb motor recovery after spinal cord injury

Authors: *A. M. LALIBERTE[1], E. KHAN[1], D. LASH-BURROWS[1], S. NASIRI[2], T. V. BUI[1]; [1]Biol., Univ. of Ottawa, Ottawa, ON, Canada; [2]Univ. of Ottawa, Ottawa, ON, Canada

Abstract: The dorsal type 3 interneurons (dI3) are a developmentally-defined population of excitatory propriospinal interneurons. Previous research has shown that permanent genetic silencing of dI3 neurons results in the suppression of functional grip development, as well as the inhibition of hindlimb locomotor recovery following thoracic spinal cord injury in mice. Given the involvement of dI3s in both grip development and motor recovery, we hypothesized that chemogenetic inhibition or activation of dI3s would impact the ability of mice to recover forelimb motor function following cervical spinal cord injury. To examine this hypothesis, Isl1-Cre:Vglut2-Flp dual recombinase mice were generated and injected with adeno-associated viral vectors conditionally expressing either EGFP (control), or hM3Dq (excitatory)/hM4Di (inhibitory) DREADD receptors in dI3 neurons between C5-T1. Using C5-C6 bilateral compression and C5 hemisection spinal cord injury models, we examined the effect of dI3 modulation on forelimb motor function on a weekly basis throughout their post-injury recovery period (up to a minimum of 6 weeks). Specifically, pellet retrieval, string pull, and grip strength behavioural tasks were performed to assess manual/bimanual coordination and strength of the affected forelimbs. Acute silencing of dI3 neurons expressing hM4Di via injections of DREADD agonist JHU37160 resulted in relatively subtle differences in forelimb function relative to saline-injected conditions. However, chronic DREADD agonism via JHU37160 in drinking water generated persistent effects on forelimb function. Given these results, the timing and duration of dI3 manipulation may be a critical factor for any potential treatment strategy involving the modulation of dI3 neurons.

Disclosures: A.M. Laliberte: None. **E. Khan:** None. **D. Lash-Burrows:** None. **S. Nasiri:** None. **T.V. Bui:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.09/C37

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation

Title: Non-invasive paired neuromodulation can facilitate upper-limb motor responses in individuals with tetraplegia

Authors: *J. OH[1], M. SCHEFFLER[1], I. TORRES[1], C. MARTIN[1], J. SHEYNIN[2], A. G. STEELE[1], V. A. DIETZ[1], T. HODICS[1], A. STAMPAS[3], D. SAYENKO[1];
[1]Houston Methodist Res. Inst., Houston, TX; [2]Dept. of Psychiatry and Behavioral Sci., Texas A&M Univ., Houston, TX; [3]McGovern Med. Sch., Univ. of Texas Hlth. Sci. Ctr., Houston, TX

Abstract: While transcutaneous spinal stimulation (TSS) can enhance functional improvements in upper limb (UL) movements for individuals with spinal cord injury (SCI), more research and clinical trials are needed to confirm and refine these findings. The efficacy of TSS interventions can vary based on the location and severity of the injury, individual factors, and the protocols used for stimulation. Transcranial magnetic stimulation (TMS), when administered in a paired manner with peripheral nerve stimulation, also shows promise in neurorehabilitation following SCI, promoting recovery of UL function. Paired use of TMS of the brain and TSS of the cervical spinal cord can strengthen sensorimotor circuits and improve motor response through associative neural potentiation. We hypothesized that TMS paired with TSS will result in synergistic neuromodulation effects on sensorimotor networks projecting to the UL muscles, when administered at specific conditioning-test intervals (CTIs). The combined approach can increase motor responses in targeted UL muscles during rehabilitation in individuals with SCI. To investigate the effects and mechanisms of this paired neuromodulation approach, we recruited ten neurologically intact subjects and three individuals with SCI. We elicited corticospinal volleys to targeted UL muscles by using TMS over the motor cortex and TSS over the C5-T1 vertebrae, using 110% and 90-100% motor threshold intensities, respectively. The CTIs between the initiation of TMS and subsequent cervical TSS varied between - 30 and 30 milliseconds. To quantify the paired TMS and cervical TSS effects, we identified the CTIs that produced the greatest increase in UL muscle responses to determine each participant's optimal pairing interval and compared corticospinal convergence across multiple segments. We observed strong facilitation of evoked motor responses when TSS was delivered close to the central motor conduction time. In addition, repeated paired protocols improved motor responses evoked by TMS in some participants with SCI, while motor response evoked by cervical TSS did not significantly change. We concluded that TSS may play a supportive role in modulating spinal circuitry at sub-motor threshold intensities, thus potentiating corticospinal projections, when coupled with TMS at the optimal timing. The combination of TMS paired with cervical TSS (applied at various, targeted cervical spinal cord levels) provides insight into how to potentially facilitate corticospinal connections and thus contribute to improved UL motor function in individuals with tetraplegia.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.10/C38

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 1R01NS119587-01A
Wings for Life Foundation Grant 268

Title: State-space modeling of the lumbar spinal cord via epidural array in a porcine model

Authors: *A. STEELE[1], G. TACCOLA[2], V. A. DIETZ[1], P. J. HORNER[1], D. SAYENKO[1]; [1]Houston Methodist Res. Inst., Houston, TX; [2]SISSA, Trieste, Italy

Abstract: Preclinical models are critical to uncovering the changes after neurological injury and evaluating methods of treatment, such as spinal cord stimulation for neuromotor rehabilitation after SCI. However, our understanding of how SCI alters the state of spinal sensorimotor networks is limited, and a more complete understanding is required for the development of new treatment modalities. To quantify changes after SCI, it is also necessary to understand how the intact spinal cord functions. The Yucatan miniature pig (minipig), which has a brain and spinal cord approximately the same dimensions as humans and has comparable gray and white matter ratios, is ideal for translating findings to human clinical trials. As translatability is essential, a state-space model is beneficial because it can be correlated to the underlying biology. To construct a state space model of the intact minipig spinal cord, we implanted a clinical-grade 32 contact four-column array in the dorsal epidural space over the lumbosacral spinal cord in four Yucatan minipigs. Evoked compound action potentials (ECAP) were recorded from the implanted array, and spinally evoked motor potentials (SEMPs) were recorded bilaterally in four hindlimb muscles during stimulation from various array locations. Somatosensory evoked potentials (SSEPs) were then recorded from the array by stimulating the right and left tibial nerves. Finally, motor evoked potentials (MEP) were recorded both epidurally and in hindlimb muscles by stimulating the motor cortex. To reduce dimensionality, principal component analysis (PCA) was performed, and a dynamic-causal model was built. The model demonstrates the underlying common mechanisms (i.e., coupling) and response characteristics of the efferent and afferent responses. The findings provide information that will help quantify the effect of SCI on the state of spinal sensorimotor networks and their function.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.11/C39

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life Foundation

Title: Non resolving neuroinflammation in chronic spinal cord injury impedes axon growth within the lesion.

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Abstract: Macrophages and microglia that infiltrate the spinal cord injury (SCI) environment remain chronically elevated. The role of non-resolving inflammation chronically after SCI has not been thoroughly investigated. Acutely after SCI, inflammation impairs axon growth and regeneration through both direct and indirect means. Whether sustained inflammation at the lesion affects axon regeneration has not been determined. Our work investigates the role of non-resolving inflammation within the lesion by depleting macrophages with the administration of the CSF1R antagonist, PLX-5622, at chronic SCI time points to examine tissue responses including axon regeneration. We apply spinal injections of retrogradely transported AAV's to knock out the phosphatase and tensin homologue protein (PTEN) as a combinatorial approach to induce axon growth after macrophage depletion and examined the contrition of inflammation to regenerative failure in chronic SCI. Our collective efforts observed that chronic macrophage depletion with PLX-5622 results in an increased growth of specific axon phenotypes within the lesioned environment including 5HT and GCRP positive axon fibers. However, combinatorial treatment with PTEN-knockout did not further improve intralesional axon growth. In addition to implicating non-resolving neuroinflammation as an inhibitor of axon regeneration, we made novel observations on the role of the chronically injured environment as a vital mediator of sustained macrophage and microglia persistence in SCI that will be further discussed.

Disclosures: A. Stewart: None. **C. Bosse-Joseph:** None. **R. Kumari:** None. **W.M. Bailey:** None. **J.C. Gensel:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.12/C40

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS117749
NIH Grant OD034314
PA department of Health Grant RFA67-127
Shriners Grant SHC-84051

Title: Genetic method to selectively lesion axons or prune axonal terminals.

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Abstract: It is well established that corticospinal tract (CST) axons have extensive axonal arborization throughout the brainstem and within spinal motor pools. How these CST terminals influence motor control through the brainstem in normal or lesioned animals remains unknown. Additionally, lesioning the CST within the pyramids or cervical spinal cord show deficits in skilled reaching. However, these CST lesions do not eliminate forelimb movements and locomotion remains intact, most likely mediated through rubrospinal, reticulospinal and propriospinal pathways. Whether or not these pathways require input from the CST to promote recovery has not been directly shown, only assumed through examination of CST sprouting into these nuclei. To better understand cortical control of brainstem motor nuclei, we have developed a genetic method to specifically and rapidly lesion axons or their terminals while inducing minimal damage to the surround neurons or tracts. To induce a genetic lesion or pruning we have modified the human CD59, a critical regulator for the formation of complement membrane attack complex (MAC). This glycoprotein normally acts to protect cells from completement mediated lysis, however, intermedilysin (ILY) released by Streptococcus intermedius specifically binds to the human but not rat form of CD59 to create a cytolytic pore. CD59 expression in rodent models have been shown to be a very effective mechanism to selectively and rapidly ablate a variety of cells in vivo, even neurons (PMC4887171 and PMID:18157141, however, we found that it was poorly transported into axons. To increase penetrance into axons, we exchanged the endogenous GPI linkage with several know to be transported into axons. We found that CD59 with the thy1.1 GPI-linkage showed good transport into axons and terminals. To determine the specificity of this genetic lesioning procedure, we injected AAV2-hCD59/thy1.1-greenlantern into the forelimb motor cortex to label CST and other cortical neurons. Two weeks later ILY was injected into either the corpus callosum or the red nucleus. We observed excellent severing and some retrograde degeneration of the callosal axons with minimal immune reaction and no identifiable damage to myelin or non-labeled axons. We also injected ILY into the red nucleus which also showed good degeneration of terminals within the red nucleus. We are presently examining the role of these CST terminals within the Red nucleus in recovery of motor function after spinal cord injury. This technique could become a useful tool to examine the functional contribution of axonal collaterals and terminals within various motor or sensory nuclei.

Disclosures: G. Smith: A. Employment/Salary (full or part-time):; Temple 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.; National Institute of Health, Shriners Hospitals. **J. Rajavong:** None. **J. Chen:** None. **X. Qin:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.13/C41

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant HD36020
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SCIRB C38338GG
DOH-C38338GG
NYS Spinal Cord Injury Research Trust Fund C32241GG
Stratton VA Medical Center, Albany, NY

Title: Electrical stimulation of sensorimotor cortex to restore function in rats with incomplete spinal cord injury: Initial results

Authors: *Y. CHEN[1], Y. WANG[2], J. S. CARP[3], B. HERRON[4], J. R. WOLPAW[5];
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Abstract: Appropriate unilateral operant up-conditioning of the soleus H-reflex (HR) can improve locomotion bilaterally in rats with incomplete spinal cord injury (iSCI) (J Neurosci 26:12537-12543, 2006). In intact rats, weak electrical stimulation (ECS) of sensorimotor cortex (SMC) increases the soleus (SOL) HR bilaterally (J Neurophysiol 108:2668-2678, 2012). We hypothesize that, when rats with asymmetrical locomotion due to lateralized iSCI are given weak ECS, the damaged locomotion heksor will shape the bilateral HR increase so as to restore locomotor symmetry (DOI:10.1113/JP283291). Under anesthesia, Sprague-Dawley rats are implanted with EMG electrodes in right SOL, a nerve stimulating cuff on right posterior tibial nerve, and epidural stimulating electrodes over left SMC; and the lateral half of either right or left spinal cord is transected at T9. Each rat receives weak SMC ECS (25 <30-µA 40-ms bipolar pulses over 1s every 10s) for 30 d. ECS has no noticeable behavioral effect. HR data are collected 24/7 throughout, and the rat practices treadmill locomotion 5d/wk. Horizontal ladder and treadmill performance are assessed before and after iSCI, and after 30 d of ECS. In 5 iSCI rats studied to date, ECS increased SOL HR to 174.9(±17.4SE)% of pre-ECS baseline (p=0.02); background EMG and M-wave size did not change. Footdrops on the horizontal ladder were 1.1(±0.2SE) before iSCI, increased to 4.8(±0.9) after SCI and pre-ECS, and fell to 2.6(±0.5) after ECS (p=0.02 for paired t-test of pre- vs post-ECS values). Treadmill data are not yet analyzed. Previous studies show that treadmill training alone does not reduce foot-drops at the end of training. These initial results indicate that ECS (like HR up-conditioning) increases HR size in

rats with iSCI; and they offer preliminary support for our hypothesis that the damaged locomotor heksor shapes this increase to restore locomotor symmetry. Further analyses and study of more rats are underway. If our initial results are confirmed, ECS might constitute a novel approach to improving locomotion impaired by iSCI or stroke.

Disclosures: Y. Chen: None. **Y. Wang:** None. **J.S. Carp:** None. **B. Herron:** None. **J.R. Wolpaw:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.14/C42

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shriners Pediatric Research Center

Title: A combinatorial approach using motor cortex stimulation and neurotrophin-3 (NT-3) treatment to alleviate spasticity and improve functional recovery after spinal cord injury.

Authors: *A. PAL[1], J. RAJAVONG[1], T. J. CAMPION III[1], G. KOMA[2], A. SPENCE[2], G. M. SMITH[1];
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Abstract: Neural plasticity is essential for recovering lost functions after brain and spinal injuries, but it can be adaptive or maladaptive. While adaptive plasticity accelerates functional recovery, maladaptive plasticity can hinder progress and lead to secondary conditions like chronic pain and spasticity, further diminishing the quality of life for affected individuals. Upper arm spasticity, a common consequence of SCI or stroke, often persists indefinitely and impedes rehabilitation, emphasizing the urgent need for effective new therapies. This study explores a novel combinatorial approach using motor cortex stimulation (MCS) and Neurotrophin-3 (NT3)-mediated plasticity to address spasticity and motor deficit associated with SCI. We hypothesized that MCS and NT-3 would enhance plasticity, restore excitatory/inhibitory balance, and improve functional outcomes. To test this hypothesis, cortical electrodes were implanted into male and female rats, with EMG electrodes placed in the *biceps* and *adductor digiti minimi*. Baseline data were collected, and rats received a C5 cervical contusion (200 kDyne), followed by randomization prior to receiving AAV2-retro-NT3 or AAV2-retro-GFP injections in the distal forelimb muscles. After recovery, rats were randomly divided in half for repetitive MCS or sham stimulation. Behavioral assays evaluated forelimb functional improvements, and overall pain was assessed using the rat grimace scale. The experimenter was blinded to treatments, and results were analyzed using t-tests and ANOVA. The combined treatment significantly improved skilled hand function compared to control groups. Animals receiving MCS and NT-3 exhibited enhanced dexterity and increased grooming. Detailed kinematic analysis of the forelimb during

locomotion showed more extended shoulder and elbow joints on average in the treatment group. Importantly, this combined treatment effectively reduced spasticity, as indicated by a significant decrease in reflex hyperexcitability. Histological analysis revealed increased axonal regrowth and neuronal survival in the treatment group, suggesting a synergistic effect of the combined therapy. These findings highlight the therapeutic potential of combining MCS with NT-3 treatment for cervical SCI, improving hand function and reducing spasticity, which are key aspects of functional recovery. By targeting both adaptive and maladaptive plasticity, the results hold significant potential for restoring the excitatory/inhibitory balance, reducing spasticity, and promoting functional recovery post-injury, thereby improving the quality of life.

Disclosures: A. Pal: None. **J. Rajavong:** None. **T.J. Campion:** None. **G. Koma:** None. **A. Spence:** None. **G.M. Smith:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.15/C43

Topic: C.11. Spinal Cord Injury and Plasticity

Support: K23-NS091440
Presbyterian Health Foundation Team Science Grant

Title: Cervical Spinal Cord Morphometrics in Degenerative Cervical Myelopathy, Quantification using Semi-automated Normalized Technique and Correlation with Neurological Dysfunctions

Authors: *F. MUHAMMAD[1], G. HAYNES[2];
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Abstract: AbstractDegenerative cervical myelopathy (DCM) is characterized by spinal cord atrophy. Accurate estimation of spinal cord atrophy is key in the understanding of neurological diseases including DCM, but its clinical application is hampered by difficulties in precise and consistent estimation. This challenge is due to significant variability of the spinal cord morphometry along the cervical spine, within and between individuals.To characterize morphometrics of a compressed spinal cord in DCM patients. We employed our semi-automated analysis framework that incorporates the Spinal Cord Toolbox (SCT) and normalization approach to effectively addressing the challenges posed by cord compression in these patients. And examined the clinical relevance of these morphometric measures.This prospective study investigated 36 DCM patients and 31 healthy controls. Using the generic spine acquisition protocol and our semi-automated analysis pipeline. Spinal cord morphometrics, including cross-sectional area (CSA), anterior-posterior (AP) and transverse (RL) diameters, eccentricity, and solidity, were extracted from sagittal T2-weighted MRI images using the Spinal Cord Toolbox (SCT). Normalized metrics were extracted from the C1 to C7 vertebral levels and compared

between DCM patients and healthy controls (HC). Morphometric data at regions of maximum spinal cord compression (MSCC) were also correlated with clinical scores including dexterity, hand grip strength, balance, gait, and mJOA scores. A subset of participants underwent follow-up scans at six months to monitor longitudinal changes in spinal cord atrophy.Morphometric data were successfully normalized with healthy human spinal cord morphometry (PAM50 database) and extracted for all participants. DCM patients showed notable reductions in CSA, AP, and RL dimensions across all vertebral levels compared to healthy controls. MSCC metrics correlated significantly with clinical outcomes like dexterity, grip strength, and mJOA scores. Longitudinal analysis indicated a decrease in CSA and worsening clinical scores in DCM patients.Our pipeline provides a reliable method for assessing spinal cord compression in DCM. Normalized spinal cord morphometrics, particularly the CSA could have potential use for monitoring severity and progression of DCM over time to guide treatment decision-making. Furthermore, our study represents the first application of the generic spinal cord acquisition protocol specifically for the detailed morphometric characterization of compressed spinal cords in DCM patients.

Disclosures: F. Muhammad: None. **G. Haynes:** None.

Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

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Program #/Poster #: PSTR111.16/C44

Topic: C.11. Spinal Cord Injury and Plasticity

Support: RS-2023-00208315
2019R1A6A1A11034536
2022M3H4A1A0409882011
RS-2023-00254156

Title: Electroceutical therapy to enhance neuronal plasticity for spinal cord injury recovery

Authors: *Y. NOH[1], J. KIM[2], S.-K. KANG[2], J. HYUN[3];
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Abstract: This study presents an innovative electroceutical approach to the treatment of spinal cord injury (SCI) using a newly developed neural interface electrode combined with a wireless electrical stimulator. Designed to deliver electrical signals throughout the spinal cord with minimal compression, this technology aims to enhance neuroplasticity and facilitate functional recovery. The electrode's low Young's modulus and full-coverage design ensure precise signal delivery and safety. In our investigation, we applied the electroceutical device to a rat model of contusion-induced SCI, delivering stimulation daily for three days after injury. Neuroanatomical evaluations performed eight weeks after implantation showed significant improvements in axonal sprouting in the treated groups compared to controls. These results indicate improved

neuroplasticity, which is essential for functional recovery in SCI. Functional outcomes were rigorously assessed using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale and the horizontal ladder walk test, with results demonstrating significant improvements in motor function. These results not only confirm the efficacy of the electrode in promoting neuroplasticity, but also suggest its potential for broader application in neurological recovery processes. In conclusion, our electroceutical design effectively promotes neuronal plasticity and functional recovery, providing a promising basis for the development of targeted, non-invasive treatments for spinal cord injury and potentially other neurological conditions such as stroke and traumatic brain injury, where recovery of motor function is critical.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.17/C45

Topic: C.11. Spinal Cord Injury and Plasticity

Support: RS-2023-00208315
2019R1A6A1A11034536
2022M3H4A1A0409882011
RS-2023-00254156

Title: Efficacy of copper oxide nanoparticles in reducing inflammation and enhancing recovery following traumatic brain and spinal cord injuries

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Abstract: Traumatic brain injury (TBI) and spinal cord injury (SCI) are debilitating conditions characterized by severe neuropathological changes including reactive oxygen species (ROS) production, inflammatory responses, and neuronal apoptosis, which collectively contribute to lasting neurological deficits. The antioxidant, anti-inflammatory, and antibacterial properties of

copper oxide nanoparticles (CuO-NP) make them a promising candidate for therapeutic intervention in such injuries. This study aimed to evaluate the anti-inflammatory and neuroprotective effects of CuO-NP on functional recovery in rat models of TBI and SCI. Severe controlled cortical impact (CCI) was used to model TBI, while a standardized contusion method was employed for SCI, with injuries inflicted using a precision impactor device. Rats were administered CuO-NP intrathecally at concentrations of 1, 5, and 10 mg/mL (designated CuO-NP1, CuO-NP5, and CuO-NP10) or phosphate-buffered saline (PBS) as a control, directly into the lesion sites. Post-treatment assessments included histological evaluation of lesion cavity size and inflammatory cell infiltration. Results indicated that CuO-NP treatment significantly reduced the cavity size and number of inflammatory cells compared to PBS controls in both models. Functional recovery was quantitatively assessed using the Modified Neurological Severity Scores (mNSS) and rotarod performance tests in TBI models, and the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale and horizontal ladder test for motor function in SCI models. Notably, the CuO-NP5 concentration demonstrated the most significant improvement in both neurological and motor functions across the 4-week and 8-week evaluation periods, respectively. These findings suggest that CuO-NP not only mitigates inflammation and neuronal damage but also significantly enhances recovery processes in traumatic CNS injuries. This study underscores the potential of CuO-NP as a novel nanopharmaceutical strategy to alleviate the complex pathophysiological sequelae following TBI and SCI, advocating further investigations into their precise mechanisms of action and long-term therapeutic benefits.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.18/C46

Topic: C.11. Spinal Cord Injury and Plasticity

Support: R01NS106908
R01NS111761
R01NS122371

Title: Targeting KCC2 to attenuate sympathetic dysfunction following complete high-level spinal cord injury

Authors: *M. J. WULF[1], V. C. BRACCHI-RICARD[2], V. J. TOM[3];
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Abstract: Heightened sympathetic reflexes (i.e., sympathetic hyperreflexia) develops after severe, high-level spinal cord injury (SCI). The resultant excessive sympathetic discharge contributes to dysfunction of organs receiving sympathetic input and leads to increased mortality. Sympathetic hyperreflexia is driven by changes within the spinal sympathetic reflex (SSR) circuit below the SCI that contribute to increased excitability of the circuit. The K^+-Cl^- cotransporter type 2 (KCC2), which helps to maintain low levels of intracellular chloride that is essential for GABAergic and glycinergic inhibition, has been implicated in exaggerated motor reflexes after SCI. Whether KCC2 plays a role in dysregulation of the sympathetic system after SCI is not yet known. We theorize that loss of KCC2 within the SSR circuit after SCI contributes to sympathetic hyperreflexia and leads to dysfunction of effector organs, such as the spleen. Our preliminary data indicate that after a complete T3 SCI - an injury that reliably results in sympathetic hyperreflexia - there was less KCC2 on the membrane of neurons within the SSR circuit than in uninjured animals. Additionally, administrating CLP290, a KCC2 enhancer drug, systemically after SCI reverses this loss of KCC2. We will perform radiotelemetric, hemodynamic recordings to examine whether treating with CLP290 after T3 SCI diminishes autonomic dysreflexia, a real-time readout of sympathetic hyperreflexia. Sympathetic hyperreflexia is also associated with loss of leukocytes in the spleen and dysimmunity. To assess if the increase in KCC2 levels in SSR circuit neurons via CLP290 treatment attenuates this, we administered CLP290 or vehicle daily starting 1 week after T3 SCI and harvested spleens 4 weeks later. Using flow cytometry, we found CLP290 treatment attenuates SCI-induced loss of leukocytes, neutrophils, monocytes, and T-cells. We are now examining if the improved leukocyte profile with CLP290 treatment enhances immunity to influenza, a leading cause of infections after SCI. CLP290- or vehicle-treated animals were intranasally administered influenza X31 4 weeks after SCI. Preliminary data suggests that CLP290 decreases the severity of infection, as indicated by reduced body weight loss. To better understand how CLP290 treatment affects the antiviral immune response after SCI, we will profile immune cells both in lungs and spleens as well as assess the level of viral clearance and viral specific responses of infected animals. This study will elucidate the role KCC2 plays in sympathetic dysregulation after SCI and identify a potential therapeutic target to attenuate the life-threatening secondary consequences of SCI.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.19/C47

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 19H05723
22H04992

Title: Supraspinal plasticity of corticofugal projections after spinal cord injury in macaques

Authors: *S. UENO[1], R. YAMAGUCHI[2], K. ISA[1], T. KAWASAKI[4], M. MITSUHASHI[1], T. ISA[3];
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Abstract: Descending fibers originating from the motor cortex are known to project to motoneurons innervating the limb muscles to induce voluntary movements of the limbs. In addition to sending the motor commands to motoneurons, higher-order circuits such as the cortico-basal ganglia and cortico-cerebellum loops also work in cooperation to properly plan the movements. Our laboratory has shown that during recovery from the spinal cord injury, plastic changes of the neural circuits compensate for the impaired functions, using macaque monkey models. In case of the milder lesions restricted to the corticospinal tract, the propriospinal neurons which spared the damage on the same side of the lesion took over the functions of injured pathways (Tohyama et al., 2017). However, neural plasticity at the supraspinal level in these animals was little reported. In this study, we focused on the supraspinal projections of corticofugal fibers in monkeys with subhemisection of the cervical cord. After motor functional recovery from the lesion, we labeled the fibers originating in the primary motor cortex in each hemisphere by injecting the anterograde viral tracers to examine the target area of their projections. As for the supraspinal areas, in case of corticofugal projection from the contralesional (affected) motor cortex, the ratios of aberrant collateral projections towards the contralateral putamen of the basal ganglia, contralateral pontine nucleus, ipsilateral lateral reticular nucleus of the medulla were increased compared to those from the ipsilesional (unaffected) motor cortex. These projections likely contribute to the activation of cortico-basal ganglia and/or cortico-cerebellar loops involving the ipsilesional motor cortex. In addition, it was found that a number of descending axons in the lesion-affected trajectory exhibited the uncrossed projections at the pyramidal decussation and descended toward the spinal cord on the opposite side of the lesion to cross the midline at the caudal to the lesion (see Rosenzweig et al. 2010). Thus, the corticofugal fibers from the lesion-affected motor cortex were found to exhibit massive plasticity at multi-hierarchical levels including the basal ganglia, brain stem, and medulla as well as the spinal cord level.

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Poster

PSTR111: Spinal Cord Injury: Plasticity and Recovery

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.20/C48

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Nialls Foundation

Title: Non-invasive modulation of chondroitin sulphate glycosaminoglycans to restore locomotor function in chronic spinal cord injury

Authors: *B. STEVENS, N. DOODY, S. CHAKRABARTY, J. C. KWOK, R. M. ICHIYAMA; Sch. of Biomed. Sci., Univ. of Leeds, Leeds, United Kingdom

Abstract: Chondroitin sulphate glycosaminoglycans (CS-GAGs) are known inhibitors of axonal regeneration and functional recovery following spinal cord injury (SCI). They are also components of perineuronal nets (PNNs) where they are involved in regulating plasticity. Chondroitinase ABC is a useful tool to digest CS-GAGs and remove PNNs in pre-clinical models of SCI, but its clinical translation remains challenging. Here we aim to repurpose 4-methylumberliforone (4-MU) to improve locomotor function in chronic SCI. 4-MU can be delivered orally, and it inhibits the synthesis of CS-GAGs and downregulates PNNs. Consequently, we have renamed 4-MU as Perineuronal Net Inhibitor (PNNi). In addition, as rehabilitation is used to enhance functional recovery in a clinical setting, we have combined PNNi with locomotor training. Rats received a moderate, 200 kdyn contusion at T9/10 prior to treatments beginning four weeks post injury to replicate the chronic phase of injury. All rats received either PNNi or a control treatment for four weeks. Additionally, a subset of rats from each group received rehabilitation for eight weeks, during which they were housed with free access to a running wheel. PNNi treatment alone led to the greatest improvement in hindlimb locomotor function amongst all groups. Rehabilitation alone also resulted in improvement, albeit not the same magnitude as PNNi alone. Interestingly, combining PNNi with rehabilitation had no additive effect compared to either treatment alone, and there was little improvement compared to untrained, control treated animals. Deeplabcut was used to analyse hindlimb kinematics during locomotion and analysis is ongoing to determine differences between treatments. Immunohistochemistry of the lumbar spinal cord is underway to analyse the local circuitry plasticity that may have facilitated the improvement in function following individual PNNi treatment or rehabilitation, and worsening function following the combination, with a view to manipulate them in future experiments.

Disclosures: B. Stevens: None. **N. Doody:** None. **S. Chakrabarty:** None. **J.C. Kwok:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jessica C F Kwok has a patent ‘Treatment of Conditions of the Nervous System’ (PCT/EP2020/079979) issued and published (WO2021078991A1).,. **R.M. Ichiyama:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.01/C49

Topic: D.01. Somatosensation – Pain and Itch

Support: CGS-D CIHR
Foundation Grant CIHR

Title: Disinhibition compromises spatiotemporal processing of touch through disruption of spinal receptive fields

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Abstract: The spinal dorsal horn (SDH) plays a crucial role in processing touch and pain signals. Different inhibitory circuit motifs in the SDH, including feedforward and lateral inhibition, influence the temporal and spatial integration of incoming signals. Spatial processing of somatosensory input is accomplished through neuronal receptive fields (RF). Specifically, spinal neurons have a center-surround RF structure formed via excitatory connections with primary afferents and inhibitory connections with other spinal interneurons. RFs have been shown to expand when synaptic inhibition is reduced, which may underlie the clinical observations that broad stimuli produce more allodynia than punctate touch in patients with neuropathic pain. Despite recent findings, the impact of RF expansion on SDH neuron or circuit function remains unclear. To begin disentangling this synaptic connectivity in the spinal cord, we built a model of spinal RFs to efficiently examine the spatial processing of different types of tactile stimuli (e.g. punctate vs. diffuse). Furthermore, we used the model to examine how different temporal features (e.g. static vs. dynamic touch) are differentially affected by disinhibition. Using experimental electrophysiology data recorded from spinal interneurons, we fit the network model to normal RF sizes and firing rates. The resulting circuit model captures the center-surround structure of spinal neuron RFs and demonstrates that RF size, as well as spatial and temporal summation, are restricted by inhibition. Neuropathic conditions, simulated by reductions in synaptic inhibition (i.e. disinhibition), reshaped RF organization and disrupted lateral and feed-forward inhibition in ways that increased spatial and temporal summation in a cell-type dependent manner. Finally, our model predicts that the effects of RF expansion are amplified in superficial lamina (e.g. I) due to the convergence of input from spinal neurons in deeper lamina (e.g. II-III).

Disclosures: L. Medlock: None. **S.A. Prescott:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.02/C50

Topic: D.01. Somatosensation – Pain and Itch

Support: 2021ZD0204404

Title: Transcriptomic and spatial organization of mouse spinal cord projection neurons

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Abstract: The spinal cord projection neurons (SPNs) convey diverse modalities of somatosensory information from the spinal cord to the brain, but their molecular and cellular heterogeneity and organization remains largely unknown. Using retrograde labeling and single-cell transcriptomic analysis, we identified 15 SPN subtypes in mice, including previously unknown GABAergic SPN subtypes, and found distinct lamina preferences in the soma distribution of most subtypes. Brain-wide mapping of SPN projections revealed distinct subtype-dependent projection patterns. The existence of GABAergic SPNs was further demonstrated by single-neuron projectome analysis and electrophysiological recording of inhibitory spinal inputs at central target brain areas. Transcriptomic data also revealed subtype-dependent expression of ion channels and G protein-coupled receptors (GPCRs) and potential ligand/GPCR-based signaling from interneurons to SPN subtypes. Finally, distinct SPN subtypes were shown to be differentially involved in pain and itch processing. This comprehensive analysis provides a framework for deciphering molecular and cellular mechanisms underlying somatosensory processing.

Disclosures: Y. Sun: None. **J. Lin:** None. **Y. Dou:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.03/C51

Topic: D.01. Somatosensation – Pain and Itch

Support: Spanish Ministry of Science and Innovation (grant PID2021-126330OB-I00 funded by MCIN /AEI /10.13039/501100011033 and by “ERDF A way of making Europe”, by the “European Union”)

Title: Central terminals of primary afferents as synchronizing element in spinal cord circuits.

Authors: *I. RIVERA-ARCONADA[1], J. LUCAS-ROMERO[2], J. A. LOPEZ-GARCIA[3]; [1]Systems Biol., Univ. of Alcala, Alcala de Henares, Spain; [2]Washington Univ. in, Saint Louis, MO; [3]Systems Biol., Univ. Alcala, Alcala Henares, Spain

Abstract: Primary afferents are responsible for transmitting the sensory information generated at peripheral receptors to the spinal cord. However, before this information reaches second-order neurons, it can be modulated by presynaptic contacts from dorsal horn neurons. These presynaptic contacts can regulate neurotransmitter release by modifying the excitability of synaptic terminals and thus the efficiency of information transmission. Using opto- and chemogenetic techniques, we wanted to investigate how changes in the excitability of primary afferent terminals can modify spontaneous activity in spinal cord circuits. These studies were carried out using in vitro spinal cord preparations from neonatal mice expressing channelrhodopsin-2 (ChR2), Archaerhodopsin-3 (ArchT) and hM4Di-DREADD in primary afferent neurons under the control of the advillin promoter. Glass suction electrodes were used to record dorsal root activity, while multi-electrode arrays were used to record the activity of neurons in the dorsal horn. An adjacent dorsal root was electrically stimulated to activate primary afferents and generate synaptic responses in both the recording root and dorsal horn neurons. ChR2 activation by light at 455nm caused a depolarization in the afferents contained within the root, together with the abolition of spontaneous dorsal root potentials (sDRPs). There was also an increase in the spontaneous firing of most dorsal horn neurons, but this enhancement was accompanied by a loss of coordination between neurons. Activation of hM4Di-DREADD with clozapine N-oxide led to a reduction in the frequency of sDRP and the firing of dorsal horn neurons, with a concomitant loss of coordinated activity. On the other hand, ArchT stimulation with light at 567nm hyperpolarized the afferents in the dorsal root and increased sDRP amplitude. The activity of dorsal horn neurons showed a moderate increase during afferent hyperpolarization with an enhancement of coordinated activity. The responses produced by the electrical stimulation of an adjacent dorsal root were inhibited by both depolarization and hM4Di-DREADD activation, but were unchanged during the hyperpolarization induced by ArchT. These results show that the ability of primary afferents to transmit information can be strongly regulated by acting at their central terminals inside the cord. Primary afferents terminals work as an essential component in maintaining coordination in the spontaneous activity of spinal circuits, contributing to adjust their excitability Financial support MICINN PID2021-126330OB-I00.

Disclosures: I. rivera-arconada: None. **J. Lucas-Romero:** None. **J.A. Lopez-Garcia:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.04/C52

Topic: D.01. Somatosensation – Pain and Itch

Support: Canadian Institutes for Health Research
FRQS
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Healthy Brains Healthy Lives

Title: The neural basis for ascending transmission of thermosensory information

Authors: *X. ZHANG[1], F. B. BOUROJENI[2], S. FERLAND[3], I. PLASENCIA-FERNANDEZ[4], A. MCFARLANE[5], K. A. BOYLE[6], J. HACHISUKA[7], F. WANG[3], Y. DE KONINCK[8], A. KANIA[9];
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Abstract: Thermosensation allows the discrimination of external temperatures and drives thermoregulatory responses. Peripheral thermoreceptors tuned to specific temperature ranges relay this information to the medullary and spinal dorsal horn. From there, it is eventually relayed to and encoded by distinct neuronal populations in the posterior insular and somatosensory cortices as well as the hypothalamus. Classic studies have identified a heterogeneous population of anterolateral tract (ALT) thermosensitive neurons in the superficial layers of the dorsal horn of the spinal cord. However, the molecular identities of such neurons remain unclear, obscuring precise insights into the functional logic of temperature relay. We recently showed that nearly half of ALT neurons of the superficial dorsal horn express the developmental transcription factor Phox2a. Interestingly, the majority of Phox2a-expressing lamina I ALT neurons have morphological and immunohistochemical properties aligned with previously identified thermosensitive ALT neurons. Therefore, we hypothesised that among all lamina I ALT neurons, Phox2a ALT neurons may constitute a unique temperature-tuned population. Single synapse retrograde rabies virus tracing from Phox2a ALT neurons and *ex vivo* patch-clamp recordings argue for direct inputs of thermoreceptor dorsal root ganglion sensory neurons. Furthermore, *in vivo* calcium imaging reveals that the majority of lamina I Phox2a ALT neurons respond to a wide range of temperatures. Amongst them, they comprise two non-overlapping populations that are selectively tuned to cool-cold and warm-hot temperature ranges. Their genetic ablation and chemogenetic manipulation suggest that they are required for temperature preference-avoidance and homeostatic/thermoregulatory responses. In line with the behavioral studies, anatomical tracing reveals that Phox2a ALT neurons channel thermosensory information into supraspinal homeostatic and discriminatory ascending streams. Together, our results suggest a coding strategy where cool and warm sensation is relayed to the brain through distinct thermal information channels. More generally, our experiments argue for the existence of an innocuous thermosensory ALT pathway, distinct from its other components that convey thermal and mechanical nociception.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.05/C53

Topic: D.01. Somatosensation – Pain and Itch

Title: Adaptation of pain-related projection neurons in acute but not chronic pain

Authors: *B. TITLE[1,2,3], E. VELASCO[4], N. ENGELMAYER[5,2], P. RAYI[6,2,3], R. YANAI[1,2,3], S. HART[7], B. KATZ[8,2,3], S. LEV[9,2,3], Y. YAROM[10,2], A. BINSHTOK[11,3,2];
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Abstract: Pain hypersensitivity is associated with increased activity of peripheral and central neurons along the pain neuroaxis. On the other hand, in other neuronal systems, increased activity leads to adaptive reduction of neuronal excitability to maintain homeostasis. Projection neurons (PNs) of spinal and medullary dorsal horns summate the activity of primary nociceptive and local central interneurons and convey it to higher centers. We show that at the peak of acute inflammatory pain, PNs reduce their intrinsic excitability and, consequently, action potential firing. When pain resolves, the excitability of PNs returns to baseline. Using electrophysiological and computational approaches, we found that an increase in potassium A-current (I_A) underlies the decrease in the excitability of PNs in acute pain conditions. We hypothesized that an I_A-induced decrease in PNs firing may restrain the output from the dorsal horn to prevent sensitization and pain chronification. Indeed, no changes of I_A in PNs were observed in chronic pain conditions, and PNs exhibit increased intrinsic excitability and firing. Our results reveal an adaptive mechanism in acute pain conditions for regulating the output from the dorsal horn network, which, if interrupted, could trigger pain chronification.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.06/C54

Topic: D.01. Somatosensation – Pain and Itch

Support: USF Early Investigator Seed Grant
Iowa Neurosurgery Departmental Grant

Title: High-frequency spinal cord stimulation-induced suppression of sensory evoked potentials in ovine mammalian model: a mechanism in pain perception?

Authors: *V. BHARMAURIA[1], Y. B. BEZCHLIBNYK[1], N. SHAHEEN[2], K. JOHARI[3], H. KAWASAKI[4], A. SINGH[5], H. OYA[4], M. A. HOWARD, III[4], O. FLOUTY[1];
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Abstract: Despite the known therapeutic efficacy of high frequency spinal-cord stimulation (hSCS) in mitigating chronic pain conditions, the precise neural mechanisms underlying its effects remain largely unknown. Research shows that hSCS may act through multiple mechanisms, including the activation of inhibitory pathways that suppress pain transmission, the modulation of neurotransmitter release, and the induction of neuroplastic changes within the spinal cord and higher brain centers. In a prior ovine study, we established that dorsal column stimulation voltages exhibit a sigmoidal relationship with stimulus-induced high gamma-band power in the somatosensory and associative cortices (Flouty et al. 2013). Here, we hypothesize that hSCS may have salient effects on cortical evoked potentials in the associative and somatosensory cortices. To this aim, three sheep underwent recordings of stimulation-induced evoked potentials using 96-channel electrocorticography (ECoG) array from the primary somatosensory and associative cortical areas during three conditions: (1) isolated tibial nerve stimulation (TNS) (2) simultaneous TNS and hSCS, and (3) isolated TNS post-hSCS. Evoked response amplitudes in all three conditions were calculated across all trials and across all channels for further analysis. We found that: (1), hSCS stimulation led to a significant suppression of the evoked response magnitudes ($p < 0.0001$). (2) This suppression was sustained into the post-hSCS period ($p < 0.0001$). (3) Furthermore, an inverse relation was observed in the degree of evoked response suppression between the somatosensory and associative cortices. These findings indicate that hSCS suppresses cortical evoked responses, with a complementing relationship between the somatosensory and associative cortices. This underscores a direct interplay of excitation and inhibition between different cortical regions during sensory processing and perception.

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Poster

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.07/C55

Topic: D.01. Somatosensation – Pain and Itch

Title: The antiallodynic effect of NF-κB inhibitor BMS-345541 is sex-dependent and modulated by the ERα receptor in the tactile allodynia induced by REM sleep deprivation in rats

Authors: *C. J. MARTÍNEZ MAGAÑA[1], J. MURBARTIÁN[2];
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Abstract: Several studies have linked sleep loss to developing pain hypersensitivity in humans and rodents. Particularly, Rapid Eye Movement Sleep Deprivation (REMSD) induces painful hypersensitivity to thermal and mechanical stimuli, but the mechanisms involved in this phenomenon remains unclear. NF-κB is a protein complex that functions as a transcription factor involved in multiple pathophysiological processes and its enhanced or dysregulated activity has been linked to arthritic, neuropathic, and migraine pain. However, their role in pain hypersensitivity induced by REM sleep deprivation has not been studied. This study aimed to determine if NF-κB is involved in establishing tactile allodynia induced by REM sleep deprivation. Female and male Wistar rats were subjected to two days of REMSD using the flowerpot multiplatform method. Von Frey filaments were used to characterize model-induced paw withdrawal threshold changes and the effect of the tested drug on mechanical sensitivity. Protein expression in the lumbo-dorsal section of the spinal cord (SC) and dorsal root ganglia (DRG; L4 and L5) was determined by Western blot. First, we confirmed that REMSD during 48 h induces mechanical allodynia in female and male rats. Compared to vehicle controls, pretreatment with a single intrathecal injection of BMS-345541, an IKK/NF-κB inhibitor (10µg before starting the REMSD protocol), prevented the establishment of mechanical allodynia in female but not in male rats. Ovariectomy, pharmacological estrogen receptor alpha (ERα) antagonism, or ERα knockdown abolished the antiallodynic effect of BMS-345541 in female rats; while, in males, a ERα agonist or overexpression of ERα allowed the antiallodynic effect of BMS-345541. The western blot analysis revealed that, in female rats, REMSD induced an increase in the expression of NF-κB proteins p50 and p65 in DRG and SC and an increase in the phosphorylated p65 form (ser 536) in DRG. In contrast, male rats subjected to REMSD only showed a moderate increase in p65 protein expression in SC. The results of this study suggest that NF-κB plays a key role in the REMSD-induced mechanical allodynia, mainly in female rats, and the pharmacological effect of BMS-345541 depends on estradiol presence and ERα receptor activity. Thus, NF-κB could be considered a potential therapeutic target for developing new strategies to combat the pain hypersensitivity related to sleep disorders.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.08/C56

Topic: D.01. Somatosensation – Pain and Itch

Support: NS135754
NS080889

Title: Early life injury alters spinal astrocyte development

Authors: *J. J. YOO[1], E. K. SERAFIN[2], M. L. BACCEI[3];
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Abstract: Neonatal tissue damage evokes both short-term and long-term changes in synaptic transmission within the dorsal horn which increase the excitability of the spinal nociceptive network. While astrocytes clearly govern synaptic function across the CNS and contribute to the sensitization of the adult dorsal horn under pathological conditions, the degree to which the structural and functional properties of dorsal horn astrocytes change with age, or as the result of neonatal injury, has never been investigated. Therefore, we sought to elucidate the effects of neonatal surgical injury on the structure and transcriptional profile of astrocytes in the developing dorsal horn. At postnatal day 3 (P3), mice expressing tdTomato in astrocytes received either a unilateral incision of the hindpaw skin and underlying muscle, or anesthesia only as a control. We then imaged individual astrocytes in the ipsilateral dorsal horn at P4, P10, and P24 using confocal microscopy in cleared tissue to allow for accurate 3D reconstruction. Using Imaris software, we quantified cell volume, domain volume, and astrocyte filament properties in 3D space. We found that astrocytes in the P3 incision group exhibit increased cell size and complexity at P4, while their size and complexity were significantly reduced at both P10 and P24 when compared to naïve controls. Next, we used mice with green fluorescent protein (GFP)-expressing astrocyte nuclei and performed bulk RNA sequencing on sorted GFP+ nuclei to identify differentially expressed genes (DEGs) in astrocytes between neonatally-incised mice and naïve controls. Our transcriptomic analysis revealed 76 DEGs between naïve and incision groups at P4, 2 DEGs at P10, and 8 DEGs at P24. Among these DEGs, we found that genes coding for extracellular matrix proteins such as *Thbs1* and *Efemp1* and cytoskeletal genes such as *Acta1*, *Acta2*, and *Tpm2* are upregulated at P4 following neonatal incision. Using gene ontology term analysis, we observed that genes involved in cell migration, cell motility, and cytoskeletal fiber organization are upregulated in incised animals at P4. Our data show, for the first time, that early life tissue damage evokes morphological and transcriptional plasticity in developing spinal astrocytes. This study harnesses the power of modern imaging and bioinformatics techniques to identify nuanced changes to astrocyte structure and gene expression after early life trauma which may influence nociceptive processing in the developing spinal cord.

Disclosures: J.J. Yoo: None. **E.K. Serafin:** None. **M.L. Baccei:** None.

Poster

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant K00NS124190
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Title: Neuromedin U Receptor Type 2-expressing Spinal Cord Interneurons Drive Neuropathic Pain

Authors: *T. S. NELSON, H. N. ALLEN, R. KHANNA;
Univ. of Florida Col. of Med., Gainesville, FL

Abstract: Neuropathic pain represents a significant clinical challenge with limited therapeutic options. Emerging evidence points to glutamatergic interneurons in the superficial dorsal horn of the spinal cord as pivotal players in the development of neuropathic pain-induced allodynia. Using unbiased spatial transcriptomics we identify a glutamatergic dorsal horn interneuron population, demarcated by the expression of *Nmur2* (coding neuromedin U receptor type 2), as a primary mediator of neuropathic pain. Using fluorescence *in situ* hybridization (FISH), we confirmed that these *Nmur2*-expressing interneurons co-localize with several markers previously associated with pathological allodynia, including *Sst*, *Npy1r*, and *Grp*. Next, we tested if *Nmur2*-expressing interneurons are both *necessary* and *sufficient* for the manifestation of neuropathic pain-like behavior via *in vivo* chemogenetics and pharmacological approaches. Pharmacological or chemogenetic activation of *Nmur2*-expressing interneurons produced neuropathic pain-like behavior in un-injured mice. Conversely, chemogenetic inhibition of *Nmur2*-expressing interneurons abolished neuropathic pain-like behavior in mice with spared nerve injury (SNI). Additionally, chemogenetic inhibition of *Nmur2*-expressing interneurons reduced glutamatergic interneuron activity in the parabrachial nucleus in neuropathic but not un-injured states. Lastly, pharmacological antagonism of the neuromedin U receptor type 2 reduced inflammatory, neuropathic, and arthritic pain. Together our results highlight *Nmur2*-expressing interneurons and the neuromedin U receptor type 2 as potential therapeutic targets for the treatment of neuropathic pain.

Disclosures: T.S. Nelson: None. **H.N. Allen:** None. **R. Khanna:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

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Program #/Poster #: PSTR112.10/C58

Topic: D.01. Somatosensation – Pain and Itch

Title: Accelerated Directed Differentiation Of Human Induced Pluripotent Stem Cell Derived Dorsal Horn Neurons for Modeling Pain Pathways

Authors: V. TRUONG, M. DAU, ***P. WALSH**;
Anatomic Inc., Minneapolis, MN

Abstract: Chronic pain is a pervasive condition that significantly impairs quality of life and poses a substantial burden on healthcare systems worldwide. Traditional pain research has predominantly utilized in vivo and in vitro rodent models, which often fail to recapitulate the human-specific pathophysiology of pain and thus may not predict clinical outcomes effectively. A critical bottleneck in advancing pain research has been the limited availability of human tissues, including dorsal horn neurons which play a pivotal role in the central processing of pain signals. In this study, we present an efficient, scalable method to generate dorsal horn neurons from human induced pluripotent stem cell (hiPSC) in only 7 days using precision-engineered media formulations without the need for transcription factor overexpression. The identity of this population is confirmed via immunocytochemistry (ICC), qPCR, and RNAscope. This population was functionally characterized by calcium imaging and medium throughput microelectrode arrays in isolation and in co-culture with hiPSC-derived sensory neurons that have been previously characterized by our group. Dorsal horn cultures express mutually exclusively BRN3A and PAX2 by ICC in a 70/30 ratio and co-express TUJ1, thereby demonstrating a highly pure neuronal culture with a ratio of glutamatergic to GABAergic dorsal horn neurons, respectively. This population of dorsal horn neurons expressed high levels of key dorsal horn genes BRN3A, LMX1B, PAX2, and PFT1A as evidenced by qPCR. RNAscope confirmed the immunohistochemistry results. Additionally, dorsal horn neurons showed spontaneous burst firing as early as two weeks in culture, reflecting network activity between the two neuronal sub-types; and their co-culture with peripheral sensory neurons demonstrated activity signatures that differed from both sensory and dorsal horn monocultures. The development of hiPSC-derived dorsal horn neurons and their integration into functional co-cultures with sensory neurons offers a sustainable and scalable source of human cells that are critical for pain drug discovery. To our knowledge, this is the first report of a syngeneic, physiologically relevant human model of the peripheral-central pain synapse; and could lead to the development of novel and specific, centrally-acting analgesics.

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. **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

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.11/C59

Topic: D.01. Somatosensation – Pain and Itch

Support: R01NS107364-01

Title: Activity dependent circuit mapping with CaMPARI2 reveals a role of spinal cord inhibitory calretinin neurons in gating mechanical allodynia induced by inflammatory injury

Authors: *M.-C. NOH[1], K. CORRIGAN[2], R. P. SEAL[3];
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[3]Neurobio., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Chronic pain can arise from diverse array of injuries and disease states. Our previous work demonstrated unique dorsal horn circuits were engaged depending on the type of injury. For instance, silencing calretinin (CR) neurons attenuated mechanical allodynia (MA) triggered by inflammatory injury, but not for neuropathic injury. By contrast, cholecystokinin (CCK) neurons were important for MA induced by both inflammatory and neuropathic injuries. Herein, we utilized activity dependent circuit mapping with CaMPARI2 and optogenetics to explore the circuit further. CaMPARI2 is a photoconvertible green calcium indicator. With coincidence of elevated intracellular Ca^{2+} and UV light, CaMPARI2 protein irreversibly converts from green to red. Taking advantage of this, we optogenetically activated CCK neuron population in the dorsal horn in both naïve and Complete Freund's Adjuvant (CFA) animals with CaMPARI2 to examine the mechanical allodynia circuits originating from CCK neuron population. As expected, vast majority of photoconverted neurons received optogenetically induced excitatory post synaptic currents. Post fixed spinal cord slices were then immunostained for CR, pax2, and the red form of CaMPARI2. In support of our previous findings, excitatory (pax2-) CR neurons were photoconverted significantly more frequently in the CFA injured mice compared to the naïve mice. Interestingly, we also observed significantly attenuated photoconversion of inhibitory (pax2+) CR neurons in the CFA group compared to the naïve. Given the highly interconnected nature of CR neuron population, we hypothesized that inhibitory CR neurons may preferentially gate mechanical allodynia induced by inflammatory injury by suppressing excitatory CR neurons. To test this, we generated $CR^{Cre}VGAT^{Flp}$ mice. Adeno-associated virus (AAV) vector containing Cre and Flp dependent hM3D were intraspinally injected to selectively activate inhibitory CR neurons in naïve, CFA, spared nerve injury (SNI) animals. Remarkably, activation of inhibitory CR neurons only significantly alleviated static and dynamic mechanical allodynia in the CFA group. In conclusion, CaMPARI2 with optogenetic tools can reveal post-synaptic targets from a genetically labeled population of neurons in an activity dependent manner. Of

particular interest, we utilized CaMPARI2 assisted circuit tracing to examine the potential gating mechanisms, or lack there of, in different injury states in a local circuit context to identify inhibitory CR neurons as a critical gate in inflammatory injury induced mechanical allodynia circuit in the spinal dorsal horn.

Disclosures: M. Noh: None. **K. Corrigan:** None. **R.P. Seal:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.12/C60

Topic: B.04. Synaptic Transmission

Support: Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research (KAKENHI) (grant number 20K18072).

Title: Methylglyoxal enhances excitatory synaptic transmission through TRPA1/V1 and ROS in the spinal dorsal horn

Authors: *T. UENO[1,2], M. YAMANAKA[1], W. TANIGUCHI[1], N. NISHIO[1], M. SONEKATSU[1], M. YUKI[1,2], R. MIYAKE[1], T. NAKATSUKA[3], H. YAMADA[1]; [1]Wakayama Med. Univ., Wakayama/ Wakayama, Japan; [2]Kishigawa Rehabilitation Hospital, Wakayama/ Wakayama, Japan; [3]Kansai Univ. of Hlth. Sci., Osaka, Japan

Abstract: INTRODUCTION: Glycation is the non-enzymatic reaction of reducing sugars and related metabolites with proteins and amino acids. Methylglyoxal (MGO), one of the glycation-related substances, has been found to be associated with pain. However, the pain mechanism of MGO remains unclear. We investigated the mechanism of action of MGO in spinal dorsal horn using whole-cell patch-clamp recordings. METHODS: Male adult Sprague-Dawley rats were used. We performed whole-cell patch-clamp recordings from substantia gelatinosa (SG) neurons. MGO was perfused for 5 min and changes in the frequency and amplitude of excitatory postsynaptic current (EPSC) were observed. RESULTS: Presynaptic effect of MGO in the spinal dorsal horn: The increase rates of the frequency and amplitude after administration of MGO were 551.5% and 112.9% (n=10). Tetrodotoxin (TTX), a voltage-gated Na^+ channel blocker, inhibits axonal conduction. In the presence of TTX, the increase rates of the frequency and amplitude after administration of MGO were 443.9% and 129.1% (n=10). In the presence of CNQX, as an AMPA/kainate receptor antagonist, no EPSC were observed during MGO application (n=5). These results indicate that MGO acts on pre-synapses and increases glutamate release. Transient receptor potential ankyrin 1(TRPA1) and TRP vanilloid1 (TRPV1) responsible for the activity of MGO: In the presence of ruthenium red, a non-selective antagonist of TRP channels, the rates of increase in frequency and amplitude after perfusion of MGO were 92.2% and 99.4% (n=10). In the presence of HC030031, a TRPA1 antagonist, the rates of increase in frequency and amplitude after perfusion of MGO were 180.6% and 102.5% (n=9). In the presence of capsazepine, a

TRPV1 antagonist, the rates of increase in frequency and amplitude after perfusion of MGO were 234.9% and 103.3% (n=8). The rates of increase in frequency and amplitude in the presence of HC030031 and capsazepine were 107.5% and 100.1% (n=8). These results indicate that both TRPA1 and TRPV1 are involved in MGO reactivity. Reactive oxygen species (ROS) associated with MGO-induced excitability of SG neuron: MGO is known to enhance the production of ROS. ROS has also been reported to act on TRPA1 and TRPV1. Next, we investigated the effect of MGO in the presence of PBN, a non-selective ROS scavenger (n = 10). There were no significant differences between before and after perfusion with MGO. Conclusion: Our study shows that MGO increases glutamate release and excites SG neurons by acting on TRPA1 and TRPV1 at the central end of primary sensory neurons. It is also revealed ROS involved in MGO-derived pain enhancing effect in spinal dorsal horn.

Disclosures: T. Ueno: None. **M. Yamanaka:** None. **W. Taniguchi:** None. **N. Nishio:** None. **M. Sonekatsu:** None. **M. Yuki:** None. **R. Miyake:** None. **T. Nakatsuka:** None. **H. Yamada:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Program #/Poster #: PSTR112.13/C61

Topic: D.01. Somatosensation – Pain and Itch

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Title: Diabetes induced mechanical allodynia circuitry in the dorsal horn with a note on methylglyoxal.

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Abstract: Mechanical allodynia is a common and debilitating persistent pain condition in which normally innocuous touch or movement become painful following injury. The dorsal horn of the spinal cord normally processes acute somatosensory information such as touch, acute pain, temperature, and itch. After injury, the spinal dorsal horn also processes mechanical allodynia. Mechanisms of central sensitization induced by injury allow low threshold mechanosensory afferents access to the nociceptive circuitry, turning touch or movement into pain. The general framework of the circuit was recently revised from a single pathway activated regardless of injury type to a more expansive network differentially activated by injury type. This was based on the identification of different but overlapping ensembles of excitatory neuron induced by inflammatory or neuropathic injuries. Here, we report the identification of the ensemble for

polyneuropathic injuries, specifically diabetic neuropathy. Initial studies indicated that the ensemble for polyneuropathy differs from the other two types of injuries. We therefore used cFos analyses combined with spatial transcriptomics at cellular resolution and identified GRP, GRPR and NPY1R as important for diabetic neuropathic pain. Using Cre lines, we targeted the inhibitory chemogenetic receptor to these populations and showed that all three are important for conveying mechanical allodynia. We next used retrograde monosynaptic rabies tracing to identify inhibitory populations that are directly connected to the GRPR neurons. Activation of these populations, NPY, PDYN and PVALB with an excitatory chemogenetic receptor attenuated mechanical allodynia in the diabetes model. Methylglyoxal is elevated by hyperglycemia in primary sensory neurons and has been implicated in the induction of mechanical allodynia in diabetes. Our analysis of the ensemble for methylgloxal induced mechanical allodynia instead resembles the ensemble for inflammatory injuries, including CALB2 and CCK neurons. This finding is consistent with data showing that methyglyoxal sensitizes TRPA1, which is the mechanism for induction of mechanical allodynia by other inflammatory models, such as low dose formalin. The work elucidates the mechanical allodynia circuitry for polyneuropathies and provides a new perspective on the role of methylglyoxal in diabetic neuropathic pain. Future work will focus on understanding the mechanisms underlying ensemble recruitment and the identification of novel chronic pain therapies that target the dorsal horn circuitry.

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Poster

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Title: Viral transneuronal tracing identifies polysynaptic spinal cord circuits that parallel the canonical anterolateral tract ascending pathway

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Abstract: A unilateral injury can result in the bilateral activation of spinal cord nociceptive circuits, a clinically relevant phenomenon (allochiria) observed in individuals, including Complex Regional Pain Syndrome (CRPS). Other studies described a polysynaptic commissural transfer of noxious information, including a mechanism by which spinal

circuits restore pain signaling post-cordotomy. Apart from their anterolateral tract connections to supraspinal centers, anatomical evidence suggests that a critical contributor to the ascending transmission of "pain", namely dorsal horn projection neurons (DH-PNs), have local axon collaterals. These collaterals may provide a route for the engagement of other functional units in an injured state, but there is limited anatomical evidence for such connections. Here we describe a transneuronal anterograde tracing approach using a conditional, DH-PN selective Cre driver line (Roome, 2020) and a Cre-dependent Herpes Simplex Virus (H129) injected into the dorsal horn of a Phox2a-Cre mouse. We also complement the polysynaptic HSV approach with an AAV-based anterograde tracer, which is limited to monosynaptic connections (Tsai, 2022). We found that H129 anterogradely labeled neurons predominate in ipsilateral Lamina X, as well as labeled neurons in the contralateral spinal cord, notably in the neck of the dorsal horn and in the lateral spinal nucleus. In addition to defining complex transneuronal spread downstream of dorsal horn projection neurons, these findings may provide an anatomical substrate for the bilateral activation of spinal cord nociceptive circuits in CRPS and other chronic pain conditions.

Disclosures: M. Jewell: None. **A.J. Crowther:** None. **A.I. Basbaum:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Title: Calcineurin and CK2 reciprocally regulate synaptic AMPA receptor phenotypes via α2δ-1 in spinal excitatory neurons

Authors: *Y. HUANG, J.-Y. SHAO, H. CHEN, J.-J. ZHOU, S.-R. CHEN, H.-L. PAN;
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Abstract: Calcineurin inhibitors, such as cyclosporine and tacrolimus (FK506), are commonly used immunosuppressants for preserving transplanted organs and tissues. However, these drugs can cause severe and persistent pain. GluA2-lacking, calcium-permeable AMPA receptors (CP-AMPARs) are implicated in various neurological disorders, including neuropathic pain. It is unclear whether and how constitutive calcineurin, a Ca^{2+}/calmodulin protein phosphatase, controls synaptic CP-AMPARs. In this study, we found that blocking CP-AMPARs with IEM-1460 markedly reduced the amplitude of AMPAR-EPSCs in excitatory neurons expressing vesicular glutamate transporter-2 (VGluT2), but not in inhibitory neurons expressing vesicular

GABA transporter, in the spinal cord of FK506-treated male and female mice. FK506 treatment also caused an inward rectification in the current-voltage relationship of AMPAR-EPSCs specifically in VGluT2 neurons. Intrathecal injection of IEM-1460 rapidly alleviated pain hypersensitivity in FK506-treated mice. Furthermore, FK506 treatment substantially increased physical interaction of α2δ-1 with GluA1 and GluA2 in the spinal cord and reduced GluA1/GluA2 heteromers in endoplasmic reticulum-enriched fractions of spinal cords. Correspondingly, inhibiting α2δ-1 with pregabalin, Cacna2d1 genetic knockout, or disrupting α2δ-1-AMPAR interactions with an α2δ-1 C-terminus peptide reversed inward rectification of AMPAR-EPSCs in spinal VGluT2 neurons caused by FK506 treatment. In addition, CK2 inhibition reversed FK506 treatment-induced pain hypersensitivity, α2δ-1 interactions with GluA1 and GluA2, and inward rectification of AMPAR-EPSCs in spinal VGluT2 neurons. Thus, the increased prevalence of synaptic CP-AMPARs in spinal excitatory neurons plays a major role in calcineurin inhibitor-induced pain hypersensitivity. Calcineurin and CK2 antagonistically regulate postsynaptic CP-AMPARs through α2δ-1-mediated GluA1/GluA2 heteromeric assembly in the spinal dorsal horn.

Disclosures: Y. Huang: None. **J. Shao:** None. **H. Chen:** None. **J. Zhou:** None. **S. Chen:** None. **H. Pan:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Topic: D.01. Somatosensation – Pain and Itch

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Title: Activation of N-methyl-d-aspartate GluN2B Initiates Neuropathic Pain after Peripheral Nerve Injury.

Authors: *Y. KIM, J. BAEK, Y. W. YOON;
Dept. of Physiol., Korea Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: The N-Methyl-D-aspartate receptor (NMDAR) GluN2B subtype is gaining attention because blocking of its activity is reported to reduce neuropathic pain with minimal side effects. However, the effectiveness of GluN2B antagonists on neuropathic pain following peripheral nerve injury and the signal transduction pathways associated with GluN2B activation remain known. After spinal nerve ligation (SNL), we investigated the temporal changes in GluN2B, as well as its phosphorylation sites at Ser1303 and at Tyr1472, calcium/calmodulin-dependent protein kinase II α (CaMKIIα) in the L5 dorsal spinal cord. To examine the interaction between GluN2B Ser1303 and CaMKII, we used co-immunoprecipitation. Mechanical paw withdrawal threshold (PWT) was measured before and after intrathecal administration of GluN2B antagonist

in SNL. Protein expression of GluN2B increased from 6 hours to 4 days and GluN2B Ser1303 phosphorylation increased up to 2 weeks. The interaction between GluN2B Ser1303 and CaMKIIα was robustly enhanced from 6 hours to 4 days after the injury. Furthermore, intrathecal administration of the GluN2B antagonist Ro25-6981 in the early phase reduced mechanical PWT. Additionally, pre-emptive intrathecal infusion of GluN2B antagonist did not induce mechanical paw hypersensitivity after peripheral nerve injury. These results demonstrate that GluN2B signaling can initiate mechanical paw hypersensitivity after peripheral nerve injury.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Title: Spinal astrocyte-derived interleukin-17A contributes to mouse bone cancer pain in either sex.

Authors: *Y. LANXING, Y. CHANG, Z. ZHOU;
fudan Univ., Shanghai, China

Abstract: <META NAME="author" CONTENT="蓝星 易">Spinal microglia and astrocytes are both involved in neuropathic and inflammatory pain, which may have display sexual dimorphism. Here, we demonstrate that the sustained activation of spinal astrocytes and astrocyte-derived IL-17A drive the progression of mouse bone cancer pain without sex difference. Chemogenetic or pharmacological inhibition of spinal astrocytes effectively ameliorates bone cancer-induced pain-like behaviors. In contrast, chemogenetic or optogenetic activation of spinal astrocytes triggers pain hypersensitivity, imply that bone caner-induced astrocytic activation is involved in the development of bone cancer pain. IL-17A expression predominantly in spinal astrocytes, whereas its receptor IL-17RA was mainly detected in neurons expressing vGlut2 and vGat. Specific knockdown of IL-17A in spinal astrocytes blocked and delayed the development of bone cancer pain, selective knockdown IL-17RA in spinal vGlut2+ or vGat+ neurons significantly blocked the bone cancer-induced hyperalgesia. Together, our findings provide evidence for a critical role of sex-independent astrocytic signaling in bone cancer pain. Targeting spinal astrocytes and IL-17A/IL-17RA signaling may offer new gender-inclusive therapeutic strategies for the management of bone cancer pain.

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Poster

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Topic: D.01. Somatosensation – Pain and Itch

Title: Intrathecal injection of Galectin-3 activates microglia and induces mechanical allodynia

Authors: *Q. ZENG[1], L. SHAN[2], K. XU[3], Z. WANG[4];
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Abstract: Intrathecal injection of Galectin-3 activates microglia and induces mechanical allodyniaAuthor*Qian Zeng, Leyan Shan, Kangtai Xu, Zilong Wang
DisclosuresQian Zeng: None. **Leyan Shan**: None. **Kangtai Xu**: None. Z**ilong Wang**: None.
AbstractEmerging studies have demonstrated spinal microglia play a critical role in central sensitization and contribute to chronic pain. Despite the identification of several mediators involved in microglia activation, the underlying mechanisms of microglial activation and its functionally diverse roles in pathological pain remain poorly understood. Here we report that intrathecal injection of Galectin-3 enhanced spinal excitatory synaptic transmission by activating microglia and inducing mechanical allodynia. Firstly, intrathecally injected exogenous Gal3 to target the spinal cord in WT mice produced acute mechanical allodynia, but not thermal hyperalgesia. And co-injected with TD-139 could block Gal3-induced mechanical allodynia. Secondly, we further determined the microglia activation in the Gal3-induced mechanical allodynia by immunostaining of Iba1, the results revealed that Gal3 induced significant microglia activation. Furthermore, the effects of microglia in Gal3-induced mechanical allodynia were confirmed by minocycline, a specific inhibitor of microglia. In our results, minocycline blocked Gal3-induced mechanical allodynia. Finally, we assessed whether Gal3 can produce an alteration in synaptic transmission in the spinal cord. We carried out an electrophysiological analysis of sEPSCs in the laminae I-IIo excitatory neurons in the SDH, by using a *vGlut2*^{Cre}: Ai9 mice line which genetically labeled excitatory neurons by expressing td-Tomato. Our recording data showed that Gal3 treatments revealed notable increases in the frequency of sEPSCs, but no statistically significant difference was observed in the sEPSC amplitude. As for sIPSC, there is no significant difference between the two groups in both frequency and amplitude. We used minocycline to test whether this enhancement of excitatory synaptic transmission induced by the treatment of Gal3 is dependent on microglia activation. We observed that bath application of minocycline (50 μg/ml) significantly blocked Gal3-induced sEPSC frequency and amplitude increase. In summary, Gal3 targets microglia and activates microglia contributing to mechanical allodynia in the spinal cord. Blockade Gal3 or microglia remarkably reduced mechanical allodynia. Our findings demonstrated that Gal3 is an endogenous microglia activator and participant in the central sensitization in chronic pain at the spinal level.

Disclosures: Q. Zeng: None. **L. Shan:** None. **K. Xu:** None. **Z. Wang:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Topic: D.01. Somatosensation – Pain and Itch

Support: R01NS087033
R01NS128403

Title: Orai3 is a key modulator of pain hypersensitivity in the spinal dorsal horn

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Abstract: Chronic pain represents a clinical challenge and a major unmet medical need**.** The molecular mechanism of chronic pain is complex and involves various receptors, ion channels, and modulators. It is well established that neuronal calcium-permeable channels are crucial for generating and maintaining pain hypersensitivity. Recently, Store-operated calcium channels, known as Orai1/2/3, have emerged as important Ca^{2+} permeable channels in neurons. Unlike calcium-selective Orai1 and Orai2 channels, Orai3 also acts as a non-selective cation channel in non-neuronal cells. Compared to extensively studied Orai1, the physiological and pathological roles of Orai3 have only recently begun to be explored. Here, we show that Orai3 is expressed in the spinal cord. Its mRNA and protein levels are up-regulated in the dorsal horn under chronic pain conditions, including the spared nerve injury (SNI), collagen-induced arthritis (CIA), and Complete Freund's adjuvant (CFA) models. Moreover, Orai3 deficiency attenuates formalin-induced nociception and CFA-induced mechanical and thermal hypersensitivity, indicating that Orai3 may play an important role in developing pain hypersensitivity. Mechanistically, Orai3 activation by 2-APB induces a Ca^{2+} response in dorsal horn neurons and results in nociception behavior. Conversely, the deletion of Orai3 attenuates 2-APB-induced currents and a Ca^{2+} response. Interestingly, thapsigargin-induced SOC entry and the 2-APB-induced Ca^{2+} entry and currents in dorsal horn neurons are not blocked by extracellular calcium and CRAC channel inhibitors, suggesting that Orai3 functions as a store-independent cation channel in dorsal horn neurons. Our study identifies Orai3 as a new Ca^{2+} permeable channel in dorsal horn neurons and a potential pain target. Our findings reveal, for the first time, the involvement of Orai3 in nociception and chronic pain, providing new insight into the molecular mechanisms of chronic pain.

Disclosures: Q. Zhang: None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

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Title: Spinal Microglia Maintain Multiple Sclerosis-Associated Neuropathic Pain

Authors: *S. LAMERAND[1], R. JAIN[1], R. DESHPANDE[1], A. ANUMOLU[1], S. STEBER[1], B. K. TAYLOR[2];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Dept. of Anesthesiol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Over half of people living with multiple sclerosis (MS) experience chronic pain that is refractive to current treatments[1]. Proinflammatory microglial activation mediates peripheral neuropathic pain in rodent models of sciatic nerve injury[2,3], but the contribution of microglia to central neuropathic pain is poorly understood. To address this gap, we hypothesized that spinal microglia maintain multiple sclerosis-associated neuropathic pain (MSNP). In adult male and female mice, some with tamoxifen-inducible CX3CR1-CreER::hM4Di-DREADD transgenes, experimental autoimmune encephalomyelitis was induced with subcutaneous injection of MOG^{33-55} and complete Freund's adjuvant (CFA) in the absence of pertussis toxin (EAE-nPTX). EAE-nPTX mice but not their control groups (CFA without MOG^{35-55} or no injections) rapidly developed plantar hypersensitivity to mechanical and cold stimuli. Next, they received either: **1)** Local microglial depletion at the spinal cord or brain with injection of liposome encapsulated clodronate (LEC) by the intrathecal (50µL/10µL, i.t.) or intracerebroventricular route (50µg/10µL), respectively; or **2)** in transgenic mice expressing inhibitory DREADDS on microglia, we injected clozapine N-oxide (CNO) by the intrathecal (60µg/10µL) or intraperitoneal (3mg/kg) route to reversibly inhibit microglia in spinal cord or the entire CNS (global), respectively; or **3)** CNS-wide depletion of microglia with a colony-stimulating factor 1 receptor (CSFR1) inhibitor, PLX3397 (600ppm in chow). **RESULTS**. First, we found that intrathecal but not intracerebroventricular LEC robustly attenuated mechanical but not cold allodynia in EAE-nPTX mice. Second, intrathecal CNO but surprisingly not intraperitoneal CNO eliminated mechanical but not cold allodynia. Third, and again surprisingly, CNS-wide microglial depletion with PLX3397 did not change hypersensitivity. We conclude spinal but not brain microglia maintain EAE-induced mechanical hypersensitivity. Our findings emphasize the complexity of site-specific immune contributions to pain in the MS population. This highlights the need for future investigations that focus on spinal microglia-specific targeting with analgesic drugs and offers insights into the challenges faced in MS pain management and treatment.

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Poster

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NIH 5R01NS095747

Title: Neuronal Wnt5a signaling contribute to NRTI-induced chronic pain

Authors: *X. LIU;
Anestheiology, Renaissance Sch. of Med. at Stony Brook Univ., Stony Brook, NY

Abstract: Antiretroviral Therapy (ART) has significantly benefited the life span and quality of patients with HIV/AIDS. However, some neurological issues like chronic pain have been shown to be closely associated with long-term ART and the underlying mechanisms remain obscure. Here, we investigated the involvement of nucleoside reverse transcriptase inhibitors (NRTIs) in chronic pain by using several conditional knockout or pharmaceutic ablation animal models. We found repeated exposure to AZT (zidovudine) or TDF (tenofovir) both significantly reduced mechanical and thermal nociceptive threshold and up-regulated proinflammatory mediator Wnt5a, cytokine IL-1β as well as reaction of spinal glial cells in wildtype mice. Pharmaceutic ablation of microglia blocked AZT- or TDF-induced nociceptive hypersensitivity, IL-1β and GFAP up-regulation without compromising Wnt5a expression. In addition, selective knockout of Wnt5a in neurons rather than ROR2 knockout in astrocytes showed similar inhibitory effect on AZT- or TDF-induced pain-like behaviors and expression of spinal IL-1β and GFAP but failed to affect microglia reaction. Furthermore, our data showed neuronal knockout of Wnt5a induced a classic anti-inflammatory cytokine IL-10 expression after AZT administration which did not be observed in mice with microglia ablation, implying neuronal Wnt5a-regulated transformation of microglia between pro- and anti-inflammatory phenotypes. Together, these results suggest that neuronal Wnt5a and microglia may be involved in NRTIs-induced neuroinflammation and chronic pain in a neuron-glia cooperative mechanism.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Title: Ib4^{+} sensory neurons-derived galectin-3 reprograms microglia in the spinal dorsal horn and contributes to neuropathic pain

Authors: *K. XU[1,2], L. SHAN[3], L. JI[4], Z. WANG[5];
[1]Dept. of Med. Neurosci., Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Department of Anesthesiology, Shenzhen People's Hospital, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, China; [3]Dept. of Med. Neurosci., Southern Univ. of Sci. and Technol., Guangzhou, China; [4]Dept. of Med. Neurosci., Southern Univ. of Sci. and Technol., Shenzhen, Guangdong, China; [5]Sch. of Med., Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: Numerous studies demonstrated under chronic pain conditions, especially neuropathic pain, microgliosis occurred and played a critical role in central sensitization. In the past two decades, several mediators that trigger microglia activation in chronic pain have been documented. However, microglia functionally diversified mechanisms in pathological pain are still unclear. Here we report that injured isolectin B4-positive (IB4^{+}) sensory neurons-derived Galectin-3 (Gal3), an animal lectin, activates and reprograms microglia in the spinal dorsal horn (SDH) and contributes to neuropathic pain. Firstly, the results of immunofluorescence and western blotting showed that Gal3 is predominantly expressed in the IB4^{+} non-peptidergic sensory neurons and significantly up-regulated in dorsal root ganglion neurons and primary afferent terminals in SDH after the partial sciatic nerve ligation (pSNL)-induced neuropathic pain model. Dorsal rhizotomy of the L4-6 spinal nerve in mice after the pSNL model indicated that Gal3 transports to the primary afferents from DRG. Additionally, Gal3 knockout decreased mechanical allodynia and microglia activation in pSNL mice. Consistently, microglia ablation with a tamoxifen-inducible deletion of microglia in Tmem119-expressing cells (Tmem119^{CreERT2};iDTR mice) largely blocked the Gal3-induced mechanical allodynia. Thirdly, RT-qPCR and western blotting showed that Gal3 treatments have enhanced inflammatory responses with TNF-α and IL-1β up-regulation in the mice SDH and primary cultured mouse microglia. Adoptive transfer experiments of Gal3 treated microglia also shown that hyperactive microglia activated by Gal3 is sufficient to produce the transient development of mechanical allodynia. Finally, using single-nuclear RNA sequencing, we found that Gal3 targets microglia and reprograms homeostatic microglia to proinflammatory MG_Lyz2 microglia, which contributes to neuropathic pain establishment. Our findings reveal that injured IB4^{+} sensory neurons-derived Gal3 reprograms microglia in the SDH and contribute to neuropathic pain. These findings provide new insights into the mechanism of microglia activation in neuropathic pain and a promising new target for treating chronic pain.

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Poster

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Posdoctoral Conahcyt 612715 to AE-Z

Title: The role of spinal oxytocin receptor in the lipopolysaccharide-induced mechanical hypersensitivity in male and female rats

Authors: *A. GONZÁLEZ-HERNÁNDEZ, G. MARTINEZ-LORENZANA, A. ESPINOSA DE LOS MONTEROS ZÚÑIGA, M. CONDES-LARA;
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Abstract: The administration of lipopolysaccharide (LPS) at the spinal level promotes neuroinflammation and subsequent sensitization to tactile stimuli, owing to the release of proinflammatory mediators by glia. Activating oxytocin receptors (OTR) at the spinal cord level promotes antinociception, probably in a biased signaling fashion. Hence, the spinal effects of oxytocin and biased OTR agonists (carbetocin or atosiban) on LPS-induced sensitization were analyzed in male and female rats. Dose-response curves were constructed for LPS and oxytocin in males and females. Carbetocin and atosiban were used to reveal the potential intracellular mechanisms induced by OTR activation. The different treatments were administered 15 min after the LPS intrathecal injection. Nocifensive behavior induced by LPS administration was analyzed using von Frey filaments to quantify the paw withdrawal threshold within 6 h after LPS administration. The administration of LPS increased sensitivity to tactile stimuli in a dose-dependent manner, with females (0.01 ng; ED_{75}) being more sensitive than males (≈10 ng; ED_{75}). While oxytocin administration decreased LPS-induced inflammation in a dose-dependent manner, females were less sensitive to oxytocin (10 nmol) than males (1 nmol); in both cases, the effect was reversed by L-368,899. Interestingly, although atosiban (1 nmol; biased OTR-Gi ligand) inhibited LPS-induced nociception in both sexes, carbetocin (1 nmol; biased OTR-Gq ligand) had no effect. Atosiban-induced antinociception was prevented by intrathecal pretreatment with pertussis toxin (an inhibitor of the Gi pathway). These data suggest that OTR activation decreases LPS-induced hypersensitivity via the OTR-Gi pathway.

Disclosures: A. González-Hernández: None. **G. Martinez-Lorenzana:** None. **A. Espinosa de los Monteros Zúñiga:** None. **M. Condes-lara:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.24/C71

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R35HL135737

Title: Microglial reprogramming contributes to inflammaraft self-maintenance and neuropathic pain

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) affects most patients undergoing chemotherapy. Microglia plays a crucial role in central sensitization and is associated with the development of pain in CIPN. Understanding the underlying mechanisms driving microglial-induced neuroinflammation could lead to the discovery of new therapies for CIPN. Here, we investigated whether signaling from cholesterol-rich membrane domains containing TLR4 (Toll Like Receptor 4), known as "inflammarafts," reprogram microglia to sustain metabolic and transcriptional changes necessary for the maintenance and perpetuation of neuroinflammation and pain. We used cisplatin treatment to model CIPN in mice, and conditional deletion of cholesterol transporters in microglia (ABCimkO mice) aiming to uncover behavioral, phenotypic, and transcriptional similarities induced by pain states characterized by sustained inflammarafts. Additionally, BV2 microglia was used to model inflammarafts in vitro, and to understand the specific metabolic pathways and gene programs adopted by microglia. Our findings revealed overlapping genome regions accessible after ATAC-seq for the transcription of genes important for TLR4 signaling, lipid raft, and droplet formation, which correlated with sustained TLR4-inflammaraft and lipid raft and droplet observed in microglia ex vivo from mice displaying mechanical allodynia. Metabolic pathways such as glycolysis were confirmed in vitro by GSEA and ECAR (extracellular acidification rate) analysis and targeting of PFKFB3 reversed the inflammaraft phenotype in vitro and in vivo, also reversing allodynia in CIPN. Additionally, we demonstrated that the metabolic switch downstream of inflammaraft appears to be mediated by ACLY (ATP citrate Lyase), controlling cholesteryl synthesis and acetyl-CoA pools. We found that the altered glycolytic flux may affect Sirt1 expression, that along with acetyl-coA contribute to histone acetylation for transcriptional regulation of inflammatory genes. These key reprogramming mechanisms hold potential for safer therapeutic interventions for CIPN and other painful conditions.

Disclosures: J. Navia Pelaez: None. **A. Patel:** None. **S. Choi:** None. **W. Ju:** None. **C. Glass:** None. **T.L. Yaksh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R01 grant NS131812
DoD grant W81XWH2110885.

Title: Intranasal and Intrathecal Administration of Conditioned Serum Alleviates Post-Stroke Pain Following Hemorrhagic Thalamic Injury

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Abstract: Stroke is a leading cause of morbidity and mortality worldwide, often resulting in central post-stroke pain (CPSP), a neuropathic pain syndrome prevalent in patients with hemorrhagic injury in the thalamic area. Despite its prevalence and impact, CPSP remains an intractable condition with limited effective treatment options. Autologous conditioned serum (ACS) has been used to treat arthritic pain. Our recent research has shown promising results with intrathecal administration of conditioned serum in resolving chemotherapy-induced neuropathic pain (Buchheit et al., 2023).
To investigate CPSP development, we established a murine model of hemorrhage-induced thalamic pain by microinjecting autologous whole blood into the unilateral ventral posterior medial nucleus (VPM) and ventral posterior lateral nucleus (VPL) of the thalamus. Mouse conditioned serum (mCS) was prepared from healthy mice, and intranasal administration was initiated either before stroke induction or at one- or four-weeks post-stroke. Sensory tests were conducted for mechanical and cold pain. Immunohistochemical staining for IBA-1 and GFAP was used to examine microglial and astrocytic reactions. Bulk RNAseq was used to examine gene expression changes in the spinal cord.
Thalamic hemorrhage induced induced CPSP in mice that lasted for months. Intranasal or intrathecal administration of conditioned serum significantly ameliorated neuropathic pain symptoms, including mechanical hyperalgesia, tactile allodynia (brush-evoked dynamic hypersensitivity), and cold allodynia (acetone-induced cold behavior) in the contralateral hind paws. The analgesic effects persisted for weeks to months. RNAseq and Histological analyses revealed that conditioned serum treatment mitigated stroke -induced activation of microglia and

astrocytes and neuroinflammation in the spinal cord dorsal horn.
Our findings indicate that autologous blood injection into the thalamus can induce profound and persistent central post-stroke pain (CPSP), accompanied by microglial and astroglial reactions. Furthermore, intranasal conditioned serum significantly alleviated neuropathic pain in the stroke model through modulation of neuroinflammation in the spinal cord.

Disclosures: R. Guo: None. **Y.D. Huh:** None. **H. Sheng:** None. **R. Ji:** None.

Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.26/C73

Topic: D.01. Somatosensation – Pain and Itch

Support: R01DK128475
K01 DK115634
AUA Scholars Fund

Title: Electrophysiological properties of sacral spinal cord interneuron in cystitis

Authors: *Y. ZHANG[1], F. LIU[2], H. HAHM[2], M. HEITMEIER[2], T. OKUDA[3], H. HEITMEIER[2], L. YANG[4], V. K. SAMINENI[5];
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Abstract: Sensory information from pelvic organs is thought to be processed by the lumbosacral spinal cord neurons. This information is thought to be relayed to the brain via projections neurons in the lumbosacral spinal cord. How this information is gated in the spinal cord is not well understood. Here we identified a specific interneuron group in the L6-S1 which is involved in the bladder somatosensation and is critical for gating the sensory information that is being transmitted to the brain. In the patch-clamp recording, the interneuron excitability was decreased in a model of cystitis. We also observed alterations in excitatory and inhibitory synaptic inputs to spinal interneurons in cystitis. Furthermore, we found that the Rostroventral Medulla (RVM) sends a monosynaptic connection to the spinal interneurons. Selectively activating the RVM descending innervated fibers in the sacral spinal cord slices, demonstrated that spinal interneurons received both excitatory and inhibitory monosynaptic inputs from RVM. In summary, the RVM can modulate the activity of interneurons in the spinal cord to process the bladder sensory information.

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Poster

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Program #/Poster #: PSTR112.27/C74

Topic: D.01. Somatosensation – Pain and Itch

Support: R01DK128475, K01 DK115634

Title: Characterization of spinal cord neurons involved in the modulation of interstitial cystitis

Authors: *F. LIU[1], Y. ZHANG[2], H. HAHM[1], M. HEITMEIER[1], H. HEITMEIER[3], T. OKUDA[4], L. YANG[5], V. K. SAMINENI[6];
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Abstract: Somatosensory signals from the end organs like bladder are relayed to the spinal cord. Our current knowledge about spinal mechanisms that are engaged in the bladder sensory processing is still largely unclear. Here we identified a subgroup of neurons in the lumbar sacral spinal cord that are important for bladder function and pain. By using chemogenetics and cell-type ablation approaches we have also identified role of these neurons in pathological bladder state caused by cystitis. Selective activation of these neurons can reduce the cystitis-induced bladder pain and bladder dysfunction. Ablating these neurons could increase the visceral hypersensitivity and bladder voiding. We have used anterograde and monosynaptic retrograde viral tracing strategies to identify the inputs and outputs of these populations. In summary, these spinal cord neurons play a significant role in encoding the bladder pain and function, which gives us a valuable insight into understanding sensory information processing of the bladder.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

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Program #/Poster #: PSTR112.28/C75

Topic: D.01. Somatosensation – Pain and Itch

Support: CarDia LX22NPO5104 European Union Next Generation EU
GACR 24-10712S

Title: Modulation of nociceptive signaling by anandamide and its precursor 20:4-NAPE in the spinal cord dorsal horn

Authors: A. BHATTACHARYYA, C. VASCONCELOS, D. SPICAROVA, ***J. PALECEK**; Lab. of Pain Res., Inst. of Physiology, Czech Acad. of Sci., Praha, Czech Republic

Abstract: Endocannabinoids, including Anandamide (AEA), and their precursors such as N-arachidonoyl-phosphatidyl-ethanolamine (20:4-NAPE), modulate nociceptive signaling via Cannabinoid (CB1) and Transient Receptor Potential Vanilloid (TRPV1) receptors in the spinal dorsal horn. This study aimed to investigate the effects of 20:4-NAPE on neuronal excitability and pain-like behavior, comparing its actions with those of AEA under various conditions. Fluorescence imaging of calcium changes in cultured dorsal root ganglion (DRG) neurons activated by repeated high K+ (30 mM), revealed a dose-dependent biphasic response to NAPE, with concentrations of 10nM-1µM inhibiting neuronal excitability mediated by CB1 and 10 µM leading to potentiation through TRPV1. AEA showed a similar trend. Inhibition of NAPE-specific phospholipase D (PLD) with LEI-401 abolished NAPE-induced changes but not those induced by AEA, indicating distinct mechanisms. *In vivo*, intrathecal NAPE administration reduced nociception at lower doses but induced hypersensitivity at higher concentrations. In spinal cord slices, 20:4-NAPE increased AEA concentration and inhibited excitatory synaptic transmission under both naive and inflammatory conditions. This inhibition was primarily CB1-mediated in naive animals but involved TRPV1 receptors after inflammation, suggesting altered mechanisms during pathological pain. Conversely, AEA application at various concentrations showed dual effects on synaptic transmission, with inhibition predominant under inflammatory conditions, highlighting the importance of endogenous AEA modulation in pain processing. Overall, these findings elucidate the complex interplay between endocannabinoids and their precursors in modulating nociceptive signaling, with implications for developing targeted analgesic therapies. Modulation of endogenous AEA production may offer more effective pain relief strategies than systemic AEA application or degradation inhibition, emphasizing the therapeutic potential of targeting the endocannabinoid system in pain management. Supported by CarDia LX22NPO5104 European Union Next Generation EU; GACR 24-10712S

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Poster

PSTR112: Spinal Circuits for Touch and Pain

Location: MCP Hall A

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Program #/Poster #: PSTR112.29/C76

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant NS072143
NIH Grant NS094438
VA I01 RX001475

Title: Germinal center formation and immunoglobulin production induce chronic nociceptive sensitization in the lumbar disk puncture model of chronic low back pain

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Abstract: Emerging evidence suggests that autoimmunity may contribute to low back pain (LBP). We previously observed in a murine lumbar spinal disc puncture (DP) model of LBP that pain-related behaviors were dependent upon mature B cells and the production of nociceptive IgM antibodies after injury. However, the time course for the development and resolution of the adaptive immune response and antibody induced nociceptive sensitization has not been determined. Using the murine DP model, we evaluated the post DP time course of nociceptive sensitization and weakness, the pronociceptive effects of intrathecal administered immunoglobulin, the accumulation of IgM and IgG in spinal cord tissue, the formation of germinal centers in paraspinal lymph nodes, and temporal changes in IgM and IgG binding against autoantigens. These experiments confirmed that; (1) wild-type (WT) DP mice developed 24 weeks of hindlimb mechanical allodynia, pinch hyperalgesia, and grip weakness, (2) spinal cord IgM levels increased at 3 weeks and peaked at 20 weeks after DP surgery, while IgG levels increased at 10 weeks and peaked at 20 weeks post DP, (3) intrathecal injection of IgM collected from WT mice at 3, 10, or 20 weeks post DP surgery was pronociceptive in DP muMT mice lacking mature B cells and antibodies, but IgM from 1 week or 34 week post DP WT mice was not pronociceptive, (4) IgG collected from WT mice at 10, 20, or 33 weeks had pronociceptive effects, but IgG from 1, 3, and 6 weeks post DP mice was not pronociceptive, (5) analyses of spinal lumbar lymph nodes demonstrated the development of germinal centers (GCs) at 3 weeks post DP, and increased numbers of large GCs were observed at 10, and 20 weeks after DP surgery, with GC formation characterized by the induction of T follicular helper cells (Tfh) and germinal center B cells, (6) WT DP mice treated with anti-CD20 antibody targeting CD20+ B cells exhibited reduced nociceptive sensitization, and (7) DP in WT mice induced the gradual increase in IgM and IgG binding activity against aggrecan, collagen II, GFAP, and NMDAR2B, peaking at 20 weeks post injury. These data further support the pronociceptive autoimmunity hypothesis for the transition from tissue injury to chronic musculoskeletal pain state.

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Poster

PSTR112: Spinal Circuits for Touch and Pain

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant DK128475

Title: The voltage-ome of the central amygdala in cystitis model mice

Authors: *T. OKUDA[1], Z. LU[3], O. ONYEGBULA[2], L. YANG[6], Y. ZHANG[4], M. KAWATANI[1], F. LIU[5], H. HAHM[5], V. K. SAMINENI[7];
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Abstract: The central amygdala (CeA) is a key regulator of pain processing. In addition to receiving nociceptive inputs from the parabrachial nucleus, the CeA integrates contextual information from multiple brain regions. This integration occurs within local CeA microcircuits formed predominantly by inhibitory GABAergic neurons before outputs are sent to downstream areas regulating pain behaviors. Recent studies have revealed a rostro-caudal heterogeneity, where the anterior and posterior subdivisions of the CeA differ in their characteristics, connectivity, and function, with evidence suggesting reciprocal signaling between them. However, deciphering the complex activity patterns within these inhibitory microcircuits using conventional techniques is low throughput and cumbersome. Here, we adapted voltage imaging in acute brain slices with optogenetics to interrogate the comprehensive voltage dynamics "voltage-ome" across the CeA neurons to perform all-optical imaging and high throughput of probing of postsynaptic connections to optogenetic stimulation. We expressed genetically-encoded voltage indicators in CeA GABAergic neurons and photostimulated terminal fibers from specific upstream brain regions. This allowed us to spatially classify CeA neurons into distinct subpopulations based on their postsynaptic response voltage profiles to specific inputs, spanning from the anterior to posterior portions of the CeA. In a mouse model of cystitis-induced visceral pain, we found that these identified CeA subpopulations exhibited differential changes in their voltage response properties. Our voltage imaging approach provides unprecedented insights into the functional heterogeneity of CeA microcircuits and their integration of distinct upstream circuits.

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Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.01/Web Only

Topic: D.01. Somatosensation – Pain and Itch

Support: SRNSFG Grant FR-21/2322

Title: Trpa1 and trpv1 channels in acute and chronic itch: assessment of hyperalgesia and allodynia

Authors: *M. TSAGARELI[1], E. E. CARSTENS[2];
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Abstract: Itch is an unpleasant sensation that provokes the desire to scratch away insects or plant spicules from the skin surface or dig out invasive parasites. While everyday acute itch reflects an adaptive mechanism to maintain the integrity of the skin, chronic itch can adversely affect the quality of life to the point of depression. In recent years, the role of various Transient Receptor Potential (TRP) channels and other receptors, including G-protein-coupled receptors (GPCRs) and protease-activated receptors (PARs), have been identified as critical in transducing itchy stimuli into action potentials that are conducted over “pruriceptive” primary afferent fibers into the nervous system. Given the importance of TRPA1 and TRPV1 in mediating itch signaling, the investigation of these ion channels has been of considerable interest for their potential roles in contributing to acute and chronic pruritis. We have recently found that acute intraplantar injection of histamine (HA) significantly reduced thermal withdrawal latency and mechanical withdrawal threshold of the ipsilateral paw. The TRPV1 channel antagonist AMG-517 pretreatment completely prevented histamine-evoked thermal hyperalgesia and mechanical allodynia. Concerning non-histaminergic mediators, chloroquine (CQ), BAM8-22, and SLIGRL that activate the receptors MrgprA3 and MrgprC11, respectively, and require coexpression of the TRPA1 channel for itch, we found that intraplantar injection of CQ, BAM8-22, and SLIGRL induced significant reductions in thermal withdrawal latency and mechanical withdrawal threshold of the ipsilateral paw. Thermal hyperalgesia and mechanical allodynia induced by these three pruritogens were significantly attenuated or prevented by the TRPA1 antagonist HC-030031, implying a critical role for TRPA1. Just recently we employed the squaric acid dibutyl ester (SADBE) model of chronic contact dermatitis carried with female C57BL/6J mice using daily topical application of SADBE for 10 days to the ventral glabrous hindpaw. This resulted in a statistically significant increase in biting and licking behavior, indicative of itch and pain, respectively. In the same mice, we tested for thermal hyperalgesia and mechanical allodynia between days 10 and 20. There were consistent reductions in thermal withdrawal latency and mechanical withdrawal threshold on the ipsilateral (SADBE treated) test paw compared to the contralateral (untreated) paw. Thus, given TRPA1 channel expression in various types of tissues and cells in itch and pain, TRPA1 is considered a novel and attractive therapeutic target for the treatment of human inflammatory diseases, itch, and pain.

Disclosures: M. Tsagareli: None. **E.E. Carstens:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.02/C78

Topic: D.01. Somatosensation – Pain and Itch

Support: Duke/Duke-NUS Collaborative Grant

Title: Neuronal mechanisms of psoriatic itch: role of sensory neuron IL17R/ERK/TRPV4 signaling.

Authors: Q. ZHANG[1], ***F. C. DIAS**[1], Q. ZENG[1], H. TAI[1], M. JANG[3], P. WANG[1], J. Y. ZHANG[2], Y. CHEN[1];
[1]Neurol., [2]Dermatol., Duke Univ., Durham, NC; [3]Neurol., Duke university, Durham, NC

Abstract: Itch represents one of the cardinal symptoms of psoriasis. Despite recent clinical studies have demonstrated the effectiveness of blocking antibodies targeting IL17 and its receptor IL17R in alleviating psoriatic itch, significant questions remain unanswered. In particular, the crucial cellular site of action and the signaling pathway of IL17/IL17R in psoriatic itch remain largely elusive. Itch sensation relies on dorsal root ganglion (DRG)/trigeminal ganglion (TG) sensory neurons that transmit pruriceptive signals from the periphery to the central nervous system. Studies have shown that IL17RA and IL17RC, two cognate receptors for IL17, express in DRG neurons. In a mouse model of psoriasis induced by imiquimod, we observed that IL17RA and IL17RC are upregulated in DRG neurons. Notably, conditional knockout (cKO) of *il17ra* or *il17rc* in sensory neurons almost abolished psoriatic itch. Furthermore, our *in vitro* assay with cultured neurons and *in vivo* assay with animal model of psoriasis demonstrated that IL17R upregulates the pruritic ion channel TRPV4 in DRG neurons *via* ERK signaling pathway. Specific deletion of *Trpv4* or suppression of phosphorylation of ERK in sensory neurons mitigated psoriatic itch. These findings suggest that the IL17R/ERK/TRPV4 signaling in sensory neurons plays a critical role in psoriatic itch.

Disclosures: Q. Zhang: None. **F.C. Dias:** None. **Q. Zeng:** None. **H. Tai:** None. **M. Jang:** None. **P. Wang:** None. **J.Y. Zhang:** None. **Y. Chen:** None.

Poster

PSTR113: Neurobiology of Itch

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Topic: D.01. Somatosensation – Pain and Itch

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Instituto de Salud Carlos III Maria de Maeztu MDM-2017-0729 and CEX2021-001159-M
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Generalitat de Catalunya 2021SGR00292
National Eczema Association NEA23-CRG184

Title: TRESK background potassium channel regulates MrgprA3$^+$pruriceptor excitability and itch sensitivity

Authors: *J. LLIMÓS-AUBACH[1,2], M. I. BAHAMONDE[1,2], A. ANDRES-BILBE[1], A. CASTELLANOS[1,2,3], A. PUJOL-COMA[1,2], H. LLUÍS[1,2], I. PALLÁS[1,2], N. COMES[1,2], G. CALLEJO[1,2], X. GASULL[1,2];
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Abstract: A subset of sensory neurons that express specific Mas-related G protein-coupled receptors (Mrgprs) and TRPs mediate pruritogen-induced chemical itch. However, the molecular mechanisms that regulate the excitability of these cells and, in consequence, itch sensitivity, are poorly understood. TRESK is a background K^+ channel that modulates the resting membrane potential, action potential firing and neuronal excitability, and it has been involved in somatosensation and pain transduction. Here, we show that this channel contributes to pruritic sensitivity and it is a potential target for the treatment of chronic itch pathologies, including different types of dermatitis, renal or liver failure and Hodgkin's lymphoma. By combining, RNA in situ hybridization, calcium imaging, electrophysiological and behavioral approaches, we found that TRESK is involved in the modulation of non-histaminergic itch. In situ hybridization experiments show that TRESK is co-expressed with MrgprA3 and MrgprD in mice sensory neurons, and with MrgprX1 in human ones. Genetic ablation of TRESK enhances firing of MrgprA3-expressing pruriceptors and acute itch in response to intradermal injection of chloroquine, while the response to histamine, BAM8-22 or LTC4 is unaffected. TRESK deletion also enhances chronic itch in mice models of allergic contact dermatitis, dry skin and imiquimod-induced psoriasiform dermatitis, where the absence of the channel produces a significantly enhanced scratching behavior that develops earlier and is more robust. Moreover, pharmacologically enhancing TRESK function, diminishes both acute and chronic itch in WT mice but not in TRESK KO animals. In summary, our data indicates that TRESK plays a role in controlling the excitability of MrgprA3$^+$ sensory neurons that mediate histaminergic-independent itch. Enhancing the channel function with specific activators constitutes a novel anti-pruritic therapeutic method that can be combined with other compounds for the treatment of non-histaminergic acute and chronic itch, for which appropriate treatments are lacking.

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Poster

PSTR113: Neurobiology of Itch

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Topic: D.01. Somatosensation – Pain and Itch

Support: National Natural Science Foundation of China (Grant No. 82271244)
Youth Innovation Promotion Association, Chinese Academy of Sciences (No. 2022266)

Title: Spinal Nmur2-positive neurons play a crucial role in mechanical itch

Authors: J. XU[1], L. LIU[2], Y. LIU[3], K. L[3], Z. JUN[4], Y. ZHU[3], ***Y. DOU**[5];
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Abstract: The dorsal spinal cord is crucial for the transmission and modulation of multiple somatosensory modalities, such as itch, pain, and touch. Despite being essential for the well-being and survival of an individual, itch and pain, in their chronic forms, have increasingly been recognized as clinical problems. Although considerable progress has been made in our understanding of the neurochemical processing of nociceptive and chemical itch sensations, the neural substrate that is crucial for mechanical itch processing is still unclear. Here, using genetic and functional manipulation, we identified a population of spinal neurons expressing neuromedin U receptor 2 (*Nmur2*$^+$) as critical elements for mechanical itch. We found that spinal *Nmur2*$^+$ neurons are predominantly excitatory neurons, and are enriched in the superficial laminae of the dorsal horn. Pharmacogenetic activation of cervical spinal *Nmur2*$^+$ neurons evoked scratching behavior. Conversely, the ablation of these neurons using a caspase-3-based method decreased von Frey filament-induced scratching behavior without affecting responses to other somatosensory modalities. Similarly, suppressing the excitability of cervical spinal *Nmur2*$^+$ neurons via the overexpression of functional Kir2.1 potassium channels reduced scratching in response to innocuous mechanical stimuli, but not to pruritogen application. At the lumbar level, pharmacogenetic activation of these neurons evoked licking and lifting behaviors. However, ablating these neurons did not affect the behavior associated with acute pain. Thus, these results revealed the crucial role of spinal *Nmur2*$^+$ neurons in mechanical itch. Our study provides important insights into the neural basis of mechanical itch, paving the way for developing novel therapies for chronic itch.

Disclosures: J. xu: None. **L. liu:** None. **Y. Liu:** None. **K. l:** None. **Z. jun:** None. **Y. Zhu:** None. **Y. Dou:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.05/C81

Topic: D.01. Somatosensation – Pain and Itch

Title: A mast cell stabilizer inhibits the induction of scratching behavior by subcutaneous administration of substance P or hemokinin-1

Authors: *H. FUNAHASHI[1], A. KANEMARU-KAWAZOE[1], Y. KOGOH[1], A. HARUTA-TSUKAMOTO[1], Y. MIYAHARA[2], T. NISHIMORI[1], Y. HIRANO[1];
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Abstract: [Introduction] Substance P (SP) and Hemokinin-1 (HK-1) are mammalian tachykinin peptides consisting of 11 amino acids in which the C-terminal of these peptides shares Met. Both peptides cause scratching behaviors when administrated intrathecally in mice; however, the difference in behavioral responses induced by subcutaneous administration of these two peptides has not been known yet. [Aims] The purpose of the present study is to examine the mechanisms by which subcutaneous administration of SP or HK-1 induces itching and whether there are differences between the two substances by pharmacological manipulations such as mast cell stabilizers will be used to measure the behavioral experiment of scratching behavior. [Results] We subcutaneously injected SP or HK-1 into the buccal region of mice and found that HK-1 exhibited only scratching behavior, whereas SP exhibited scratching and wiping behaviors. Next, HK-1 and SP were injected subcutaneously after administration of a mast cell stabilizer cromoglicic acid dissolved in PBS. Scratching behavior of induced by HK-1 or SP was decreased, while SP-induced whipping behavior was unchanged. [Conclusion] These results suggest that HK-1 and SP are pruritogens and mast cells are involved in pruriceptive processing after subcutaneous administration of HK-1 or SP.

Disclosures: H. Funahashi: None. **A. Kanemaru-Kawazoe:** None. **Y. kogoh:** None. **A. Haruta-Tsukamoto:** None. **Y. Miyahara:** None. **T. Nishimori:** None. **Y. Hirano:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.06/C82

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R01 DA048153

Title: The CB_2 receptor as an anti-pruritic target in experimental pruritus

Authors: *A. M. RECK[1], S. G. KINSEY[2];
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Abstract: Introduction: Pruritus is the experience - akin to pain - that induces one’s desire to scratch. Current therapeutic strategies for reducing pruritus are limited by ineffectiveness and

adverse side effects, prompting a need for novel treatments. Despite evidence of the antipruritic effects of various cannabinoids, clinical translation is hindered by their CB_1 receptor mediated cannabimimetic effects, particularly in studies that used higher doses of cannabinoids seen to also cause locomotor deficits. The goal of the present study was to test the hypothesis that the cannabinoid receptor full agonist, WIN 55,212-2, reduces compound 48/80-induced scratching via a mechanism requiring the CB_2 receptor. **Methods:** Adult male and female C57BL/6J mice were administered WIN 55,212-2 (0.1, 0.3, 1, or 3 mg/kg, i.p.) 50 min prior to compound 48/80 (50 μg in 100 μL, s.c.), and immediately placed in sound-attenuating chambers and video recorded for 30 min. Hind paw scratching time was quantified by a blinded observer. To probe potential receptor mechanism, a separate cohort of naïve mice were administered the CB_1 receptor-selective antagonist rimonabant (3 mg/kg, i.p.), the CB_2 receptor-selective antagonist SR144528 (3 mg/kg, i.p.), or vehicle 10 min prior to WIN 55,212-2 (0.3 mg/kg, i.p.). The antipruritic effects of the CB_1 receptor positive allosteric modulator ZCZ011 (10 or 40 mg/kg, i.p.) or the CB_2 receptor selective agonist JWH-133 (10 or 20 mg/kg, i.p.) were determined. Finally, the established antipruritic effects of WIN 55,212-2 were tested in male and female CB_2 (-/-) and CB_2 (+/+) littermates. **Results:** WIN 55,212-2 (≥0.3 mg/kg, i.p.) reduced compound 48/80-induced scratching without inducing locomotor deficits. The antipruritus achieved by WIN 55,212-2 administration (1 mg/kg) was seen to be attenuated by either rimonabant or SR144528 pretreatment. The CB_1 receptor positive allosteric modulator ZCZ011 was also tested versus compound 48/80-induced scratching. ZCZ011 had no effect, but JWH-133 reduced pruritus. Finally, WIN 55,212-2 reduced scratching in CB_2 (+/+) wildtype mice, but this antipruritic effect was absent in CB_2 (-/-) mice. **Conclusions:** WIN 55,212-2 reduced experimentally induced scratching, and this antipruritis was blocked by either chemical antagonism or genetic deletion of the CB_2 receptor. Similarly, CB_2 receptor selective agonism reduced scratching, further supporting a CB_2 receptor mediated mechanism of cannabinoid-induced antipruritus.
Acknowledgments: This work was supported financially by the National Institute on Drug Abuse [NIH R01 DA048153] and the UConn Center for Advancement in Managing Pain.

Disclosures: A.M. Reck: None. **S.G. Kinsey:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.07/C83

Topic: D.01. Somatosensation – Pain and Itch

Title: An insular cortical circuit required for itch sensation and aversion

Authors: *X. ZHANG[1], L. HUANG[2], B. LI[3];
[1]Sun Yat-sen Univ., Guangzhou, China; [2]Dept. of Pathophysiology, Sun Yat-Sen Univ., Guangzhou, China; [3]Zhongshan Sch. of Med., Sun Yat-Sen Univ., Guangzhou City, China

Abstract: Itch encompasses both sensory and emotional dimensions, with the two dimensions reciprocally exacerbating each other. However, whether a shared neural circuit mechanism governs both dimensions remains elusive. Here, we report that the anterior insular cortex (AIC) is activated by both histamine-dependent and -independent itch stimuli. The activation of AIC elicits aversive emotion and exacerbates pruritogen-induced itch sensation and aversion. Mechanistically, AIC excitatory neurons project to the GABAergic neurons in the dorsal bed nucleus of the stria terminalis (dBNST). Manipulating the activity of the AIC → dBNST pathway affects both itch sensation and itch-induced aversion. Our study discovers the shared neural circuit (AIC → dBNST pathway) underlying the itch sensation and aversion, highlights the critical role of the AIC as a central hub for the itch processing, and provides a framework to understand the neural mechanisms underlying the sensation and emotion interaction.

Disclosures: X. Zhang: None. **L. Huang:** None. **B. Li:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.08/C84

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R01AR074062
Stanley Glaser Foundation Research Award UM SJG 2019-18

Title: Investigating the involvement of Kappa Opioid Receptors in the central amygdala in itch

Authors: *D. PAVLENKO, T. AKIYAMA;
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Abstract: The central amygdala (CeA) has been shown to be involved in both up and down-regulating itch. This bidirectional regulation is thought to be due to its highly heterogeneous population. One such population is the kappa-opioid receptor (KOR) found in both the central and peripheral nervous system (PNS). KOR is a G-protein coupled receptor (GPCR) and its activation in the CeA leads to downstream inhibition. While previous research focuses on the antipruritic role of KOR in PNS and the spinal cord, this study specifically explored its role in the CeA. To study this, OPRK-flox mice were injected bilaterally with AAV-hsyn-Cre-tdTomato to knockout the receptor within the CeA (while control mice received AAV-hsyn-tdTomato). Then a battery of behavior tests was run including spontaneous itch, thermal sensitivity (Hargreaves test), mechanical sensitivity (von Frey test), formalin test, and hot plate. For the spontaneous itch test, mice were recorded for 30 minutes, and the number of scratches was counted. The experimental group exhibited a significant increase in the amount of scratching compared to the control group, suggesting an inhibitory role of KOR in the CeA in itch signaling. However, in both thermal and mechanical sensitivity test, there was no significant difference in paw withdrawal latency and threshold between the experimental and control

groups. Interestingly, number of jumps (hot plate test) and time spent paw licking (formalin test) significantly decreased in the experimental group, consistent with previous findings implicating KOR in the CeA in pain facilitation. Overall, KOR in the CeA could inhibit itch signaling as seen in the PNS and spinal cord.

Disclosures: D. Pavlenko: None. **T. Akiyama:** None.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.09/C85

Topic: F.04. Neuroimmunology and Neurovirology

Support: Allen Discovery Center
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LEO Pharma
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NIAMS Grant AR082315
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NIAID Grant AI176660

Title: The Role of Histamine-4 Receptor (H4R) in Histaminergic Itch

Authors: *K. SONG[1,2,3,4,5], Z. WANG[6,2,3,4,5], B. S. KIM[6,2,3,4,5];
[1]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Mark Lebwohl Center for Neuroinflammation and Sensation, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Marc and Jennifer Lipschultz Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [5]Allen Discovery Center for Neuroimmune Interactions, Icahn School of Medicine at Mount Sinai, New York, NY; [6]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Itch is an uncomfortable sensation that triggers the desire or reflex to scratch. The most well-described form of itch is histamine-mediated, or histaminergic, itch. Histamine can activate itch-specific neural pathways to mediate the transmission of itch from the periphery to the brain. Classically, the histamine-1 receptor (H1R) is the most well-characterized; H1R is expressed on itch-sensory neurons (pruriceptors) and its blockade is a therapy for histaminergic itch and resultant hives. Antihistamines targeting H1R, however, have shown limited efficacy in treating most pruritic diseases. Recently, the histamine-4 receptor (H4R) has been suggested to be involved in inflammation and its antagonism was shown to attenuate itch. However,

mechanisms by which H4R mediates itch remain poorly defined. Herein, we explore the precise contributions of H4R in histaminergic itch. We have shown that the cytokine IL-33 amplifies histaminergic itch by acting on mast cells. Our results suggest that this is primarily dependent on intact H4R signaling.

Disclosures: K. Song: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novo Nordisk, Regeneron Pharmaceuticals. **Z. Wang:** None. **B.S. Kim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ABRAX Japan, KliRNA Biotech, Locus Biosciences, Recens Medical, Patent for the use of JAK1 inhibitors for chronic pruritus, Patent pending for the use of JAK inhibitors for interstitial cystitis. F. Consulting Fees (e.g., advisory boards); 23andMe, ABRAX Japan, AbbVie, Almirall, Amgen, Arcutis Biotherapeutics, Arena Pharmaceuticals, argenx, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Clexio Biosciences, Eli Lilly and Company, Escient Pharmaceuticals, Evommune, Galderma, Genentech, GlaxoSmithKline, Granular Therapeutics, Incyte Corporation, Innovaderm Research, Janssen, Kiniksa, LEO Pharma, Maruho, Novartis, Pfizer, Recens Medical, Regeneron Pharmaceuticals, Sanofi, Septerna, Triveni Bio, Vial, WebMD.

Poster

PSTR113: Neurobiology of Itch

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.10/C86

Topic: D.01. Somatosensation – Pain and Itch

Support: Supported by a grant from the Interdisciplinary Center for Clinical Research within the faculty of Medicine at the RWTH Aachen University FOR 2690: Translationale Pruritusforschung, Projektnummer 350193106

Title: Temporal discharge patterns in human Polynociceptors possibly shape itch versus pain sensation

Authors: *A. FIEBIG[1], A. TROGLIO[2], A. MAXION[3], B. NAMER[1];
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Abstract: Itch and pain are distinct sensations originating from peripheral nerve signals, yet the mechanisms behind their differential signaling remain elusive. Mechano-sensitive C-fibers (CM) respond to both itch and pain-inducing substances, as well as to noxious heat. Recent studies suggest that CM neurons may differentiate between itch and pain through variations in temporal action potential discharge patterns. Our analysis of temporal discharge patterns in humans stimulated chemically and by heat sheds light on how these sensations are encoded, revealing the

complexity of nerve fiber signaling in itch and pain perception. Using microneurography, we recorded action potentials from single afferent CM-fibers in human volunteers, stimulated by various chemical substances and heat. We analyzed the data with the traditional marking methods and Spike2 spike sorting algorithms. Identified fibers exhibiting a " slow bursting" discharge pattern were further examined using the "spikelet method". Visualized using 2D heatmaps, the analyzed data provided insights into action potential patterns. We could show that most CM fibers exhibited either "slow bursting" or "non-bursting" temporal discharge patterns in response to various substances, regardless of pruritogens. Further examination highlighted distinct differences, with slow bursting patterns showing higher regularity. Chemical bursts displayed higher regularity and shorter spikelet length compared to heat-evoked spikelets, with chemicals predominantly eliciting itch sensations. Our analysis reveals distinct temporal discharge patterns in human CM fibers in response to chemical pruritogens and painful heat stimuli. These findings suggest modality-specific temporal encoding in human C-polynociceptors, guiding therapeutic interventions for chronic itch and pain conditions.

Disclosures: A. Fiebig: None. **A. Troglio:** None. **A. Maxion:** None. **B. Namer:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: /

Topic: D.03. The Chemical Senses

Support: Cognitive Neuroimaging Centre (D821/CoNiC)

Title: Sensory symphony: Enhancing neurophysiological recordings with a gustatory stimulator device

Authors: *R. BHUVANAKANTHAM[1], P. PADMANABHAN[1], B. GULYAS[1], S. MISHRA[2]; [1]Nanyang Technological Univ., Singapore, Singapore; [2]Synaptic Delver Pte. Ltd., Singapore, Singapore

Abstract: Despite the advancement in neuroimaging and neurotechnology, there is a gap in the research and exploration of human taste physiology. Research showed the role of the secondary gustatory area (i.e., orbitofrontal, medial prefrontal cortex and cingulate areas) in subjective pleasantness of taste. Moreover, the correlation between the primary gustatory cortex (i.e., insula and opercular cortex) and subjective intensity, viscosity, temperature and the fat texture of foods have been reported in studies. To explore this field, a method such as recoding of gustatory evoked potentials and gustatory evoked magnetic fields showed a more precise description of gustatory cortex activity. A unique taste delivery method is required to generate gustatory ERPs, which enables precise stimulus control in real-time using imaging. The availability of a commercial gustatory stimulus device for the delivery of different tastants in these neurophysiological examinations using EEG, MEG, MRI and so forth is not sufficient. Hence,

we aim to design and develop an electronically controlled tastant delivery system to study the role of various tastants in modulating the primary and secondary taste areas in the brain. We designed and developed the prototype of a computer-controlled peristaltic pump-type tastants delivery system. The tastants stimulator was successfully verified for its functionality in delivering a stimulus, signalling the flow and time parameters in recordings and applicability with MEG and fMRI devices without generating any artifacts. Furthermore, the corresponding responses from the brain showed different patterns for different taste categories. fMRI region-of-interest analysis displayed different mean cortical activity across all tastants in the gustatory cortex. Across hemispheres, salty, sour and bitter solutions elicit higher cortical activity in the right hemisphere, which suggests lateralization preference of neural processing for these tastants.

Disclosures: R. Bhuvanakantham: None. **P. Padmanabhan:** None. **B. Gulyas:** None. **S. Mishra:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.01/C87

Topic: D.03. The Chemical Senses

Support: MEXT/KAKENHI 21H00812

Title: Diurnal rhythms of sweet preference & bitter aversiveness in rats

Authors: *H. MOCHIZUKI-KAWAI[1], T. XIONG[2], S. SHIMODA[2], T. KAWAI[1], M. TOYOSHIMA[2], R. TACHIHARA[2], K. YAMADA[2];
[1]Inst. of Food Res., Natl. Agr. and Food Res. Organization (NARO), Tsukuba, Japan; [2]Univ. of Tsukuba, Tsukuba, Japan

Abstract: Most organisms have developed endogenous 24-h rhythms that adapt physiology and behavior to the appropriate time window in each day. These rhythms have been reported in the endocrine system and metabolism associated with eating; however, the rhythm of taste preference remains unclear. We hypothesized that diurnal rhythms might also exist in taste sense, and control food intake. Thus, we examined the licking behaviors of rats in response to five different tasting solutions across light-dark phase to determine changes in their taste preference and aversiveness. The taste stimuli used in this experiment were NaCl (0-500 mM) for salty, sucrose (0-750 mM) for sweet, monosodium glutamate (0-200 mM) for umami, citric acid (0-50 mM) for sour, and denatonium (0-5 mM) for bitter. Citric acid and denatonium were dissolved in a 250mM sucrose solution to motivate licking behavior. We measured the number of licks for 10 seconds from the first licking action of the sipper tube, repeating this 16 times with a series of four concentrations for each taste. Lick ratios were calculated relative to the baseline number of licks for distilled water (salty, sweet, umami) or 250 mM sucrose solution (sour, bitter) during each 10-s test session. The lick ratios increased during the dark phase for highly concentrated

sucrose solutions. In contrast, rats showed a decreased lick ratio for moderately concentrated denatonium solution. No differences were observed between the light-dark phase for the other three tastes. Our data revealed that rats exhibited increased preferences for sweet tastes and aversion to bitter tastes during the dark phase. The present results suggest that taste function may have evolved to optimize feeding behavior by increasing sensitivity to sweet and bitter tastes during the active phase, resulting in efficient energy intake and safe food selection. In addition, we are investigating the relationships among lick ratio, eating related hormones (Leptin, Ghrelin), and the light cycle.

Disclosures: H. Mochizuki-Kawai: None. **T. Xiong:** None. **S. Shimoda:** None. **T. Kawai:** None. **M. Toyoshima:** None. **R. Tachihara:** None. **K. Yamada:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.02/C88

Topic: D.03. The Chemical Senses

Support: Project HOGAR Faculty Grant

Title: Responses to sucralose are associated with meal pattern parameters to high energy diet in female but not male rats

Authors: C. GONZALEZ THONG, *Y. TREESUKOSOL;
CSU Long Beach, Long Beach, CA

Abstract: Taste influences what foods and fluids we select and prefer to consume. Taste phenotype has been associated with components of ingestive behavior in humans and rats. When rats are presented with water and sucralose (an artificial sweetener) in a two-bottle intake test, as sucralose concentration increases some rats drink more sucralose than water (sucralose preferers; SP) but others drink less (sucralose avoiders; SA). It has been previously documented that the SA/SP phenotype predicts differences in responses to some “sweet” and “bittersweet” compounds. Here, male and female rats categorized for sucralose status were single-housed in food intake monitoring cages and presented chow or a high energy diet (HE) for daily 23-h test sessions. For females, SP rats initiated fewer but larger meals to HE than same-sex SA rats, but no group differences were observed for males. These differences suggest orosensory stimulation are enhanced and/or sensitivity to postoral inhibitory cues elicited by HE diet are dampened in SP rats compared to SA females. In contrast, no group differences were observed for intake nor meal pattern parameters to chow indicating the sucralose taste phenotype does not predict mechanisms that drive non-palatable diet intake. Together, these findings suggest that sucralose acceptance may serve as a biomarker for differences in oral and post-oral cues in female rats.

Disclosures: C. Gonzalez Thong: None. **Y. Treesukosol:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.03/C89

Topic: D.03. The Chemical Senses

Support: University of Vermont - Startup Lab Funds

Title: Insulin and dopamine receptors modulate sweet sensitivity in drosophila melanogaster

Authors: *C. ARNTSEN, M. STANLEY;
Univ. of Vermont, Burlington, VT

Abstract: Christian Arntsen[1], Molly Stanley[11]University of Vermont, Department of Biology, Burlington, VT
Insulin and dopamine receptors modulate "sweet" sensitivity in *Drosophila melanogaster*
Hunger can directly modify the sensitivity of food-sensing chemosensory cells as a way to encourage food consumption when nutrients are low. Previous work in *Drosophila melanogaster* demonstrates that gustatory receptor neurons (GRNs) are directly impacted by food deprivation in a way that increases the detection and consumption of sugars. Dopamine plays a role in this process, but potential modulation via canonical hunger/satiety hormones, like insulin, in these gustatory cells has not been described. Using the single-cell transcriptomics database Fly Cell Atlas, we find insulin receptor (*InR*) and dopamine receptor (*DopEcR*) expression in cells identified as "sweet"-sensing GRNs based on expression of *Gustatory Receptor 64f (Gr64f)*, a sugar receptor. Inactivated insulin signaling only in "sweet"-sensing GRNs via *InR[DN]* expression or *InR*-RNAi knockdown led to increased sucrose sensitivity in the fed state, but not the starved state. *DopEcR* RNAi knockdown resulted in the opposite effect, decreasing sucrose sensitivity, but only in the fed state. *In vivo* calcium imaging of "sweet"-sensing GRNs revealed that sucrose-mediated responses were subtly enhanced without InR signaling in the fed state, matching the behavior. In contrast, overactive insulin signaling via *InR[CA]* expression in "sweet"-sensing GRNs resulted in suppression of sucrose-mediated responses in the starved state. Overall, we conclude that *InR* and *DopEcR* signaling in "sweet"-sensing GRNs reciprocally impacts sucrose sensitivity in a state-dependent manner.

Disclosures: C. Arntsen: None. **M. Stanley:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.04/C90

Topic: D.03. The Chemical Senses

Support: KAKENHI 23K24515
KAKENHI 23K18366

Title: Ghrelin regulates excitatory synaptic transmission from the insular cortex to the nucleus of the solitary tract in the rat

Authors: *A. WAKABAYASHI[1], Y. NAKAYA[2], M. KOBAYASHI[3];
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Abstract: The rostral part of the nucleus of the solitary tract (rNST) receives gustatory inputs via the facial, glossopharyngeal, and vagus nerves. In addition to these ascending inputs, the rNST receives descending projections from higher brain regions including the insular cortex (IC). The dysgranular and granular IC around the middle cerebral artery involves neurons that respond to gustatory stimulation, and therefore, the descending projections from the IC to the rNST are likely to regulate gustatory information processing. However, little is known about how IC inputs regulate neuronal activities in the rNST, in which glutamatergic and GABAergic neurons reside. This study aimed to investigate the synaptic strength of IC◊rNST in glutamatergic and GABAergic/glycinergic neurons, and examined the effect of ghrelin, an orexigenic gastric peptide hormone secreted when caloric intake is limited. We performed whole-cell patch clamp recording from slice preparations including the rNST in vesicular GABA transporter-Venus transgenic rats that received AAV5-hSyn-ChR2 (H134R)-mCherry injection into the IC. We first confirmed that glutamatergic neurons receive inhibitory inputs from rNST GABAergic/glycinergic neurons by paired whole-cell patch-clamp recordings. Blue light stimulation induced monosynaptic excitatory postsynaptic currents in both glutamatergic and GABAergic/glycinergic rNST neurons. We found that the amplitude of optogenetically induced EPSCs in glutamatergic neurons tended to be larger than that in GABAergic/glycinergic neurons. Bath application of ghrelin suppressed the amplitude of optogenetically induced EPSCs in GABAergic/glycinergic neurons. These results suggest the IC-induced facilitation of glutamatergic outputs from the rNST, which is potentiated by ghrelin via suppression of inhibitory inputs to glutamatergic neurons.

Disclosures: A. Wakabayashi: None. **Y. Nakaya:** None. **M. Kobayashi:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

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Program #/Poster #: PSTR114.05/C91

Topic: D.03. The Chemical Senses

Support: NIH Project 2R01DC007703-06
NIH Project 5R01DC006666-07

Title: Taste preexposure blunts a nonlinear change in consumption

Authors: *A. P. PATEL[1], D. A. SVEDBERG[2], D. B. KATZ[3];
[1]Dept. of Psychology, [2]Neurosci., [3]Dept Psychol, Brandeis Univ., Waltham, MA

Abstract: Rapid Attenuation of Neophobia (RAN) has been described as a stimulus-specific increase in preference modulated by experience. Previously observed only in a single-taste context, we report simultaneous AN to Sucrose, Saccharine and salt, using 'preference score' in a brief-access task (BAT, Monk et al. 2014). This supports that changes in taste consumption are a general feature of a rat's first tasting session. However, it is unclear if this effect is truly experience-dependent or is perhaps modulated by contrast-dependent effects (for instance, between the tastes or compared to water). We reasoned that if this effect reflects an AN-like effect of exposure, then pre-exposure to sucrose would blunt it. We observed a nonlinear increase in consumption to sucrose across the first brief portion of the 1st session. Indeed, pre-exposure to sucrose eliminated the significant increase in sucrose licking in the BAT. A similar nonlinear change was observed in cortical taste responses, suggesting that this is a phenomenon whereby taste coding and behavior become more consistent with experience (Flores et al., 2022; Svedberg, unpublished). Whether this change represents the coding becoming more accurate, and whether consumption converges on a taste-specific steady state, is still unclear. Still, we provisionally propose that changes in taste consumption and neural coding can be thought of in terms of experience-dependent reductions of variability, as exposure constrains both behavioral and electrophysiological responses, making them more consistent.

Disclosures: A.P. Patel: None. **D.A. Svedberg:** None. **D.B. Katz:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.06/C92

Topic: D.03. The Chemical Senses

Support: NIDDK Grant R00DK119586
Brain Research Foundation Seed Grant BRFSG-2023-09

Title: Fan SfN abstract 050524

Authors: *W. FAN[1], N. R. SCIOLINO[2];
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Abstract: The central noradrenergic system modulates sensory perception according to attention and arousal state; however, its impact on the taste system is poorly understood. The primary gustatory cortex (GC), a key brain region in taste perception, receives a prominent noradrenergic input from the locus coeruleus (LC). LC neurons are transiently activated when an animal discovers and approaches food, but are subsequently suppressed during consumption. To

understand how these dynamics influence taste processing in the GC, we used a miniature microscope system to optogenetically activate LC axons while monitoring either the spontaneous or taste-evoked calcium activity in individual GC neurons. Our results demonstrate that brief activation of LC axons during sucrose approach predominantly enhanced GC excitatory response to sucrose consumption. In contrast, brief activation of LC axons during sucrose consumption produces a mix of enhancing and suppressive effects. Further, we found that sustained tonic activation of LC axons during a taste sampling session broadens the tuning of GC neurons to four basic tastes (sweet, salty, sour, bitter), suggesting a reduction in taste discriminability. Collectively, these findings imply that the inherent dynamics of LC neurons, i.e., activation preceding consumption and suppression during consumption, may optimize cortical taste processing. To determine if activation of the LC-GC pathway influences taste-related behavior, we optogenetically stimulated the GC-projecting LC axons as mice chose between water or an unfamiliar sweet solution (saccharine). We found that stimulation of the LC-GC pathway significantly increased preference for the unfamiliar taste and facilitated its familiarization in subsequent tests. Taken together, our findings uncover a novel role for LC neurons in modulating cortical taste encoding, as well as taste perception and learning.

Disclosures: W. Fan: None. **N.R. Sciolino:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.07/C93

Topic: D.03. The Chemical Senses

Support: GT15942
NIH R01 DC006666
NIH R01 DC007703
NIH T32 MN019929

Title: Investigating the Neural Signals Driving the Consummatory Response in Rats

Authors: *N. BAAS-THOMAS[1], A. MAHMOOD[2], Y. WANG[2], D. B. KATZ[3];
[1]Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; [2]Brandeis Univ., Waltham, MA; [3]Dept Psychol, Brandeis Univ., Waltham, MA

Abstract: The gustatory system is an ideal model with which to study the neural processes guiding ethologically-relevant behavior. When a taste stimulus reaches the tongue, the gustatory system has one basic goal - to determine whether that stimulus should be consumed or expelled from the mouth. Rats produce discriminative orofacial movements reflecting the reaching of this decision. Several labs have investigated neural circuitry leading to the rejection of a tastant, an investigation which is aided by the conspicuous nature of the primary aversive-related orofacial movement, gapes. Here, we aim to better understand the signals guiding and reflecting the

decision to ingest a palatable tastant, by developing a machine learning classifier capable of discriminating individual aversive and ingestive-related orofacial movements from electromyographic (EMG) activity of the jaw opener (anterior digastric) muscle. Notably, this classifier successfully identified a distinctive subtype of tongue protrusion, a behavior associated with ingestion, with a similar onset time to gaping. We compared this onset to taste processing in primary gustatory cortex (GC), where taste responses progress through three firing-rate "epochs". The transition to the late epoch has previously been shown to act as a modulatory signal to initiate gaping, and preliminary results indicate a similar temporal correlation between the third epoch transition and the decision to ingest. We propose that the late epoch transition guides the selection and initiation of consummatory-related behaviors by modulating brainstem motor circuitry. These findings will ultimately enrich our understanding of how GC sensory information is transformed into appropriate motor responses.

Disclosures: N. Baas-Thomas: None. **A. Mahmood:** None. **Y. Wang:** None. **D.B. Katz:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.08/C94

Topic: D.03. The Chemical Senses

Support: NIH RO1 DC006666
NIH RO1 DC 007703
Swartz Foundation Computational Neuroscience Fellowship
Brandeis Computational Neuroscience Training Grant Fellowship

Title: Investigating intra-state dynamics in taste-evoked gustatory cortex responses in rats

Authors: *V. CALIA-BOGAN[1], A. MAHMOOD[1], D. B. KATZ[2];
[1]Brandeis Univ., Waltham, MA; [2]Dept Psychol, Brandeis Univ., Waltham, MA

Abstract: Cortical taste processing is comprised of a sequence of discrete states of ensemble neural firing (Mahmood et al., 2023). Sudden coherent between-state transitions, detected using Hidden Markov Modelling (HMM), have been observed in both Gustatory Cortex and Basolateral Amygdala. While "constant-emission" HMMs (i.e., models that treat activity within a state as constant plus noise) describe neural population activity better than either trial-averaged PSTHs or Drift-Diffusion models (Sadacca et al., 2016; Baez-Santiago et al., 2016), the assumption of perfectly stationary activity is likely too simplistic. In particular, we hypothesize that the notable trial-to-trial state duration variability is governed by hitherto overlooked intra-state dynamics—that differences in the speed with which within-state dynamics reach "completion" determine differences in state duration. To test this hypothesis directly, we have employed a suite of advanced computational methods for estimating moment-to-moment firing rate changes in taste-evoked population activity. Preliminary analyses show that taste-evoked

activity of the neural ensemble within single states is in fact non-homogenous, and that intra-state dynamics are indeed present within cortical activity. Future work will test for an explicit link between these intra-state dynamics and the duration of taste-processing states. Regardless, our results will strongly constrain the set of theoretical models capable of generating such dynamics and therefore performing taste-related decision-making. Characterization of these dynamics will further enhance our understanding of the requisite properties of the underlying system.

Disclosures: V. Calia-Bogan: None. **A. Mahmood:** None. **D.B. Katz:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.09/C95

Topic: D.03. The Chemical Senses

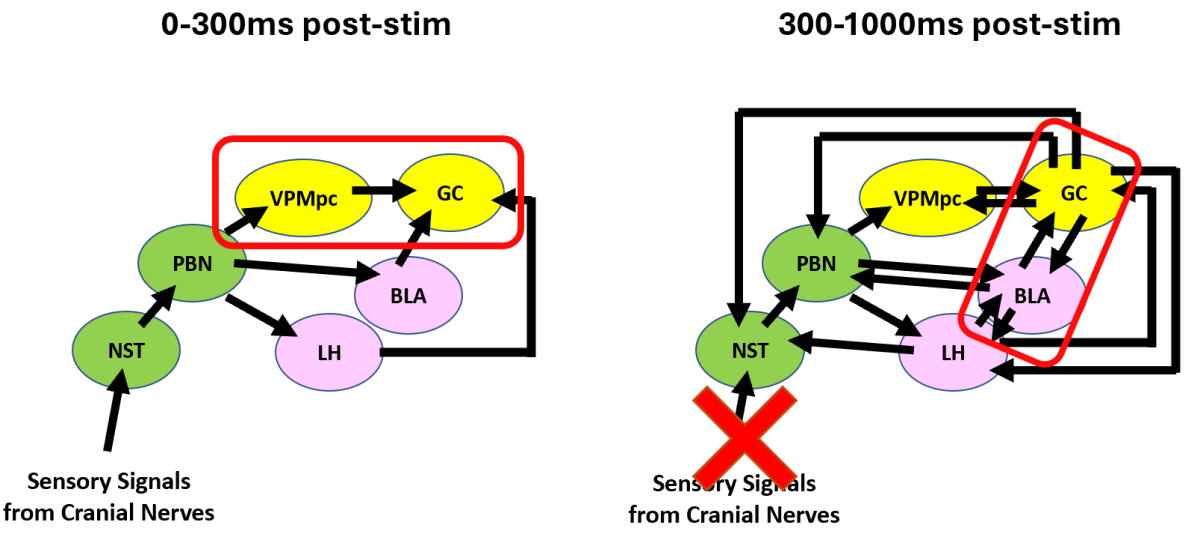
Support: NIH R01 DC006666
NIH R01 DC007703
Swartz Foundation Computational Neuroscience Fellowship

Title: Basolateral Amygdala and Gustatory Cortex interact bidirectionally during taste processing in rodents

Authors: *A. MAHMOOD[1], D. B. KATZ[2];
[2]Dept Psychol, [1]Brandeis Univ., Waltham, MA

Abstract: Taste responses in Gustatory Cortex (GC) and Basolateral Amygdala (BLA) evolve as sequences of 3 states during the ~1.5 seconds following tastant delivery onto the tongue of the rat. GC activity reflects first somatosensation, next identity (taste quality), and then palatability across these 3 states; BLA activity, meanwhile, reflects both identity and palatability during the 2nd state. Previous work using symmetric connectivity (i.e., cross-coherence) measures has shown that GC and BLA remain strongly interacting throughout all 3 states, while the "pattern" of interaction between them changes with each state. However, the assumption of symmetric back and forth flow of information inherent in the above analyses is likely simplistic. To test this assumption and thereby gain a better understanding of systemic taste processing, we used multi-region electrophysiology and characterized the dynamics of the directional influence between BLA and GC using lags in the population state transitions, spectral Granger Causality, and Poisson Generalized Linear Modelling (GLM). Our analyses reveal that: 1) GC and BLA begin recurrently interacting after 300ms following stimulus delivery—at the onset of identity coding; 2) this recurrence is likely initiated by the onset of BLA->GC influence, while the GC->BLA influence is uniformly strong; 3) GC and BLA influence one another in different frequency bands, a fact that suggests functionally distinct projection populations between GC and BLA; and 4) this suggestion of functionally distinct projection populations is confirmed using Poisson

GLMs. These results further characterize GC->BLA modulation during the evoked taste response and show that BLA and GC are bidirectionally interacting only during the period from 300ms post-stimulus delivery till generation of the taste-evoked behavioral response.



Disclosures: A. Mahmood: None. **D.B. Katz:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.10/C96

Topic: D.03. The Chemical Senses

Support: whitehall foundation

Title: Central circuit for taste-dependent salivation

Authors: *G. PARK[1], J. YE[2], H. LEE[1];
[1]Northwestern Univ., Evanston, IL; [2]Westlake Lab., Westlake Univ., Hangzhou, China

Abstract: Taste input is a strong trigger for salivation. When we feast on a meal with tangy tomato sauce, flavorful drinks, and sweet desserts, the food stimulates our eyes, nose, and mouth, leading to salivation. This physiological response involves the activation of salivary glands situated in the cervical and mandibular regions, which produce saliva to facilitate the digestive process. The parotid glands are activated by preganglionic fibers of the glossopharyngeal nerve from the inferior salivatory nucleus. For the submandibular and sublingual glands, parasympathetic innervation starts in the superior salivatory nucleus. However, there is limited evidence showing how the sensory aspects of taste integrate with the salivary circuit. The

detection of tastants initiates a complex neural cascade, contributing to our taste experience. This process begins with ganglion neurons transmitting signals from the tongue, entering the brain through connections with the rostral nucleus of the solitary tract (rNST) in the brainstem; the information ultimately reaching the taste cortex. Here, we delineate how the neural circuit for taste sensation converges onto the preganglionic salivary neurons to regulate salivation.

Disclosures: G. Park: None. **J. Ye:** None. **H. Lee:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.11/C97

Topic: D.03. The Chemical Senses

Support: Fellowship 233646 CONAHCYT
UNAM-DGAPAIN203518

Title: Dynamic Protein Changes in Aversive Taste Conditioning: Insights from GAP-43 and Synaptophysin in Memory Retrieval and Extinction

Authors: *L. E. GRIJALVA[1], R. G. PAREDES[2], G. N. QUIÑONEZ-BASTIDAS[3];
[1]Programa de Licenciatura en Fisioterapia, Univ. Estatal de Sonora, Unidad Académica Hermosillo, Hermosillo, Mexico; [2]ENES/INB UNAM, Querétaro, QRO, Mexico; [3]Ctr. de Investigación y Docencia en Ciencias de la Salud, Univ. Autónoma de Sinaloa, Culiacán, Mexico

Abstract: Understanding the neural mechanisms underlying the evocation, extinction, and maintenance of taste memory is crucial for elucidating the intricate processes involved in learning and memory. The model we employed allows for the analysis of numerous variables, with well-defined circuits implicated in the process. Notably, the amygdala and the gustatory cortex (GC) are among the key structures implicated in conditioned taste aversion (CTA). In our investigation, we delved into the plastic changes occurring during the formation, evocation, and extinction of appetitive and aversive taste memories. Prior research has underscored that memory consolidation is not the sole focus; rather, the extinction of established memories plays a pivotal role in adaptive behavior and overcoming maladaptive responses. Understanding the dynamics of memory extinction is crucial for developing interventions to mitigate the impact of aversive experiences and promote adaptive learning processes in memory formation, elicits plastic alterations, including heightened levels of proteins recognized as markers of neuronal plasticity, such as growth-associated protein 43 (GAP-43) and synaptophysin (SYN). Here, we investigated the role of GAP-43 and SYN proteins in these processes. We examined changes in GAP-43 and SYN expression induced by the formation of aversive and appetitive taste memories using immunohitochemical techniques in male rats. During memory recall, we observed a significant increase in GAP-43 expression in the basolateral amygdala (BLA), particularly in the context of

aversive memory. On the other hand, during memory extinction, we detected a significant increase in GAP-43 expression in the overtraining group in the central amygdala, along with an increase in SYN expression in both the basolateral and central amygdala. These results suggest a crucial role of GAP-43 and SYN in mediating the plastic changes underlying memory extinction processes. Our findings underscore the importance of memory extinction in adaptive behavior and offer potential avenues for interventions to mitigate aversive experiences and promote adaptive learning.

Disclosures: L.E. Grijalva: None. **R.G. Paredes:** None. **G.N. Quiñonez-Bastidas:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.12/C98

Topic: D.03. The Chemical Senses

Support: 5R01-DC018227-05

Title: Taste processing in a mouse model of frontotemporal dementia

Authors: *Y. ZHENG[1,2], J. BLACKWELL[3], A. FONTANINI[4];
[1]Stony Brook University, Neurobio. & Behavior, Stony Brook, NY; [2]Dept. of Neurobio. and Behavior, SUNY Stony Brook, Stony Brook, NY; [3]Neurosci., Brown Univ., Providence, RI; [4]Neurobio. and Behavior, Dept. of Neurobio. & Behavior, SUNY Stony Brook, Stony Brook, NY

Abstract: Frontotemporal dementia (FTD) is the second most prevalent form of presenile dementia. Patients with FTD show a pathological sweet tooth and decreased ability to identify flavors. The chemosensory deficits in FTD may be related to damage of the gustatory insular cortex (GC) as the insular cortex is one of the primary targets in FTD disease progression. Little is known about how circuitry changes in GC lead to deficits in taste processing in FTD. The goal of this project is to test the hypothesis that the taste deficits are present in a mouse model of FTD and the deficits are related to abnormal patterns of neural activity in GC. Inclusions of the transactivating response region (TAR) DNA binding protein (TDP-43) are a significant pathological feature in 50% of FTD cases, thus we chose a transgenic mouse model overexpressing human TDP-43 with a Q331K mutation (TDP-43^{Q331K}). To assess taste deficits, we relied on a taste-based two alternative forced choice (2AFC) task probing the ability to discriminate sucrose/NaCl mixtures. TDP-43^{Q331K} mice made more mistakes and showed significant deficits in the mixture discrimination 2AFC task compared to non-transgenic control mice. To assess deficits in GC taste processing, we relied on electrophysiological recordings using chronically implanted tetrodes in alert TDP-43^{Q331K} and non-transgenic control mice. Activity in GC was probed as mice licked multiple gustatory stimuli (sucrose 200mM, NaCl 50mM, quinine 0.5mM, citric acid 10mM). The proportion of taste selective neurons in TDP-

43^{Q331K} mice decreased over time compared to control mice. Palatability processing was impaired in TDP-43^{Q331K} mice compared to control mice. Principal component analysis confirmed that population activity dynamics evoked by the different gustatory stimuli were more similar in TDP-43^{Q331K} mice than in control mice. Classification analysis showed that taste decoding decayed faster over time in TDP-43^{Q331K} mice relative to control mice. Overall, these results demonstrate taste deficits in a mouse model of FTD and provide evidence for altered taste processing in GC of TDP-43^{Q331K} mice compared to control mice.

Disclosures: Y. Zheng: None. **J. Blackwell:** None. **A. Fontanini:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

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Program #/Poster #: PSTR114.13/C99

Topic: D.03. The Chemical Senses

Support: NIDCD R01 DC013770

Title: Integration of thalamocortical and limbic circuits in mouse gustatory cortex

Authors: *A. C. MCHALE-MATTHEWS, A. MAFFEI;
Neurobio. and Behavior, SUNY Stony Brook, Stony Brook, NY

Abstract: Neurons in the primary gustatory cortex (GC), a subregion of the insula, play an important role in taste identity, taste processing, and anticipation of hedonic value. Previous work in our laboratory has shown that the parvicellular region of the ventral posteromedial thalamic nucleus (VPMpc, also known as the gustatory thalamus), as well as the basolateral amygdala (BLA), have overlapping afferent fields and converging inputs in the GC, suggesting that GC neurons can act as direct integrators of sensory and hedonic information. However, little is known regarding the location, and/or cell identity of neurons that receive convergent inputs from VPMpc and BLA, nor the synaptic properties modulating the integration of these inputs. In this study, we optogenetically activate both VPMpc and BLA afferents to the GC in acute slice preparations of male and female mice while recording from postsynaptic neurons in whole cell patch clamp. Our preliminary results show that BLA inputs modulate VPMpc responses onto GC neurons, and that this modulation depends on the properties of BLA synaptic responses. When BLA inputs onto GC neurons are facilitating in response to a burst of stimuli, VPMpc responses converging onto these same neurons are amplified. On the other hand, when BLA bursts of responses show short term depression, converging VPMpc inputs are attenuated. These presynaptic properties seem specific to cortical layer and cortical granularity in the GC. Overall, these preliminary findings provide new insights into thalamocortical and limbic integration in the mouse GC.

Disclosures: A.C. McHale-Matthews: None. **A. Maffei:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

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Program #/Poster #: PSTR114.14/C100

Topic: D.03. The Chemical Senses

Support: NIDCD R01 DC013770
NIDCD R01 DC020722
NIDCD R01 DC019827

Title: Amygdalar Circuits for Sensory Satiety

Authors: *A. BERENJI KALKHORAN[1,2], A. FONTANINI[1,2], A. MAFFEI[1,2];
[1]Stony Brook Univ., Stony Brook, NY; [2]Neurobio. and Behavior, SUNY, Stony Brook Univ., Stony Brook, NY

Abstract: Sensory satiety, a non-homeostatic habituation behavior occurs when repeated exposure to a certain stimulus (food) result in the decline in preference of that food, and dynamical modulation of palatability. Disfunction in sensory satiety could potentially lead to the emergence of hyperphagia, a common factor in certain types of obesity. In the gustatory portion of insular cortex (GC) which is involved in taste processing and taste related decision making, a population of neurons express an anorexigenic neuropeptide called gastrin releasing peptide (GRP). Preliminary data from our lab shows these neurons send a dense projection to the basolateral amygdala (BLA), a region which is involved in taste palatability and regulation of feeding behaviors. Previous work from other groups reported that amygdalar infusion of GRP in rats and mice reduced food intake, implicating this region of the brain and GRP signaling in the control of eating. Here, we examine the hypothesis that GC neurons expressing GRP modulate BLA circuits through the activation of neurons expressing GRP receptors (GRPR+ neurons), and this interaction is mediating satiety by modulating taste palatability. We first determined the neurochemical and physiological identity, and the anatomical distribution of GRPR neurons in BLA with immunohistochemistry and RNAscope in situ hybridization. We also assessed how GRP affects the membrane properties of BLA-GRPR+ neurons using patch clamp recordings in acute slices containing BLA. We report that BLA GRPR+ neurons are heterogeneous and include both excitatory and inhibitory neurons. Bath application of GRP changed parameters associated with synaptic transmission and membrane properties of BLA-GRPR+ neurons in a cell type dependent manner. Results from this study advances our understanding of GRP-GRPR signaling at the GC-BLA input and highlights changes in circuits regulating feeding providing novel targets for medical interventions.

Disclosures: A. Berenji Kalkhoran: None. **A. Fontanini:** None. **A. Maffei:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.15/C101

Topic: D.03. The Chemical Senses

Support: NIH F31-DC019518

Title: Neurosteroid Activity in the Gustatory Cortex and its Effects on Taste-Dependent Behavior

Authors: *P. YEVOO, A. FONTANINI, A. MAFFEI;
Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: Food consumption is essential for survival, but maladaptive feeding behaviors can modify the reward value of food and food-related cues. Studies show neurosteroid signaling alter consummatory behaviors. Specifically, allopregnanolone produced hyperphagic effects in both human and animal subjects, but the neural circuits and mechanisms underlying these effects remain unknown. The anterior IC - also known as the gustatory cortex (GC) - is involved in processing taste, the expectation of reward, and decision-making regarding feeding. The GC has also been implicated in disordered eating behavior. This evidence suggests that it is an ideal regional circuit to investigate how neurosteroids such as allopregnanolone may modulate food intake. Our work investigates the neurosteroid-mediated tonic inhibitory circuitry in the insula and its influence on consummatory behavioral profiles in adult mice. Using allopregnanolone, we investigate the contribution of tonic inhibition to consummatory behavior and GC circuit excitability. Neurosteroid-sensitive extrasynaptic $GABA_A$Rs contain the δ subunit. We utilized immunohistochemistry and fluorescence in-situ hybridization to examine the expression patterns of δ-$GABA_A$Rs. We showed that these receptors are localized on both inhibitory and excitatory cells in GC in different proportions. To explore the receptor's functionality, we employed patch-clamp recordings from neurons in acute slices to test the magnitude of tonic inhibitory currents. Our data show a cell-type-dependent modulation of tonic currents following neurosteroid application. We then assessed the effect of local neurosteroid infusion on sucrose preference and show infusion of allopregnanolone into GC alters sucrose preference in a cell-type-dependent fashion. These data support the hypothesis that neurosteroid signaling in GC plays a central role in modulating taste preference and may influence ingestive behaviors. Revealing how neurosteroid signaling modulates cortical activity may provide novel biomarkers for diagnosing, treating, and preventing neuropsychiatric disorders characterized by impaired motivational states and inhibitory control.

Disclosures: P. Yevoo: None. **A. Fontanini:** None. **A. Maffei:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.16/C102

Topic: D.03. The Chemical Senses

Support: NIDCD F32 DC018485
NIDCD R01 DC019827

Title: Inhibitory plasticity controls gustatory cortical circuit refinement

Authors: *H. C. SCHIFF[1], A. MAFFEI[2];
[1]SUNY - Stony Brook, Stony Brook, NY; [2]Neurobio. and Behavior, SUNY Stony Brook, Stony Brook, NY

Abstract: Sensory cortical circuits undergo protracted maturation during the postnatal period. Postnatal circuit refinement is heightened during critical periods, shaped by experience, relies on synaptic plasticity, and involves maturation of inhibition. The proper development of cortical circuits is crucial for the emergence of complex functions including sensory perception, decision-making, and cognition. Early taste experience at the time of weaning influences the development of taste preferences and cortical inhibition in the gustatory cortex (GC), the primary sensory region for taste (Schiff et al, 2023). However, there is little information regarding the time course of maturation in brain regions related to taste including GC. Here, we delineate the cellular and circuit properties of GC that change over the course of postnatal development. We used whole-cell patch-clamp electrophysiology, immunohistochemistry, and channelrhodopsin-assisted circuit mapping to track postnatal maturation of GC in male and female mice. We recorded from GC pyramidal neurons in young (P17-24), juvenile (P35), and young adult (P56) mice and observed an increase in spontaneous inhibitory postsynaptic currents (IPSCs) in the absence of changes in spontaneous excitatory postsynaptic currents (EPSCs), suggesting developmental shifts in excitatory-to-inhibitory ratio. The changes in synaptic inhibition were accompanied by increases in parvalbumin (PV) fluorescence intensity in PV-expressing interneurons (PV^+ INs) and accumulation of perineuronal nets on PV^+ INs. We also observed morphological changes in pyramidal neurons, and a transient decrease in their intrinsic excitability. Ongoing analyses will determine the map of synaptic connectivity between PV^+ INs and pyramidal neurons in GC and assess possible developmental changes in connectivity. These results suggest that GC circuit refinement is associated with maturation of inhibition, specifically PV^+ INs. Understanding the sequence of events regulating postnatal refinement of gustatory cortical circuits will allow us to better understand how the interaction of cellular mechanisms, nutrition, and early life sensory experience may influence healthy brain development and neurodevelopmental disorders.

Disclosures: H.C. Schiff: None. **A. Maffei:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.17/C103

Topic: D.04. Interoception

Support: NSERC

Title: A scopolamine methyl nitrate (SMN) model of conditioned disgust behaviour in rats

Authors: *G. LAKE[1,2], L. WANG[1], M. AL-KHUDAIRY[1], M. KAVALIERS[1,3,2], K.-P. OSSENKOPP[1,2];
[2]Grad. Program in Neurosci., [1]Univ. of Western Ontario, London, ON, Canada; [3]Psychology and Neurosci., Univ. of Guelph, Guelph, ON, Canada

Abstract: The conditioned gaping response can be observed in rats when they are exposed to a distinct context that has been paired with an emetic drug/toxin. Over multiple pairings, exposure to the distinct context alone will evoke the gaping response. Rats are a non-emetic species, meaning that they cannot vomit, however, they are still capable of perceiving nausea. The primary sign of emesis in rats is gaping, it involves the rapid opening and closing of the mouth, tends to occur about 5-7 times per bout, and showcases the interior of the mouth. Such patterns of exposure to a distinct context followed by the presence of nausea and/or vomiting, are most commonly seen in chemotherapy patients is referred to as anticipatory nausea (AN). The current study aimed to determine if scopolamine methyl nitrate (SMN), a quaternary derivative of scopolamine, can induce the conditioned gaping response in rats when they are exposed to a distinct context. As previous literature suggests it may elicit AN, SMN was chosen as the emetic stimulus. To investigate the ability of SMN to evoke the conditioned gaping response, we used adult male Long Evans rats (n = 32), and two dosages of SMN (0.5 mg/kg and 1.0 mg/kg, intraperitoneal [i.p.]). Alongside, lithium chloride (LiCl, 127 mg/kg, i.p.) and sodium chloride (NaCl, 0.9%, matching dose to LiCl, i.p.) serving as controls, LiCl is commonly known to elicit nausea in rats. Treatment groups were weight-matched to account for any influence of body weight. Following treatment administration, rats were placed into the distinct context and remained undisturbed for 30 minutes in the dark, during which their behaviour was videotaped. Extinction (drug-free) trials were completed as well. Four conditioning and four extinction trials were completed each 72 hours apart. All of the video recordings from the conditioning and extinction trials were blindly scored for the frequency of the conditioned gaping response. On conditioning trials 3 and 4, and extinction trials 1, 2, and 3, the LiCl treatment group gaped significantly more than the NaCl, low SMN, and high SMN treatment groups ($p < .05$). The gaping responses displayed by both SMN treatment groups did not differ significantly from that of the NaCl group on any of the conditioning and extinction trials. Currently, in the literature LiCl is primarily utilized to induce gaping in rats, therefore, interest in using alternative emetic stimuli to induce the gaping response is growing. The findings from this study suggest that SMN treatment is not an effective stimulus to induce the conditioned gaping response in rats using this AN paradigm.

Disclosures: G. Lake: None. **L. Wang:** None. **M. Al-Khudairy:** None. **M. Kavaliers:** None. **K. Ossenkopp:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.18/

Topic: D.03. The Chemical Senses

Support: NIDDK Grant R00DK119586
Brain Research Foundation Seed Grant BRFSG-2023-09

Title: Locus coeruleus noradrenergic neurons modulates cortical taste processing

Authors: *N. R. SCIOLINO;
Physiol. and Neurobio., Univ. of Connecticut, STORRS, CT

Abstract: The central noradrenergic system modulates sensory perception according to attention and arousal state; however, its impact on the taste system is poorly understood. The primary gustatory cortex (GC), a key brain region in taste perception, receives a prominent noradrenergic input from the locus coeruleus (LC). LC neurons are transiently activated when an animal discovers and approaches food, but are subsequently suppressed during consumption. To understand how these dynamics influence taste processing in the GC, we used a miniature microscope system to optogenetically activate LC axons while monitoring either the spontaneous or taste-evoked calcium activity in individual GC neurons. Our results demonstrate that brief activation of LC axons during sucrose approach predominantly enhanced GC excitatory response to sucrose consumption. In contrast, brief activation of LC axons during sucrose consumption produces a mix of enhancing and suppressive effects. Further, we found that sustained tonic activation of LC axons during a taste sampling session broadens the tuning of GC neurons to four basic tastes (sweet, salty, sour, bitter), suggesting a reduction in taste discriminability. Collectively, these findings imply that the inherent dynamics of LC neurons, i.e., activation preceding consumption and suppression during consumption, may optimize cortical taste processing. To determine if activation of the LC-GC pathway influences taste-related behavior, we optogenetically stimulated the GC-projecting LC axons as mice chose between water or an unfamiliar sweet solution (saccharine). We found that stimulation of the LC-GC pathway significantly increased preference for the unfamiliar taste and facilitated its familiarization in subsequent tests. Taken together, our findings uncover a novel role for LC neurons in modulating cortical taste encoding, as well as taste perception and learning.

Disclosures: N.R. Sciolino: None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.19/C104

Topic: F.08. Food and Water Intake and Energy Balance

Support: NSF Award Number 2332375
UVM Startup Funds

Title: Amino acids activate parallel chemosensory pathways in Drosophila melanogaster

Authors: *G. DAVIS, M. STANLEY;
Biol., Univ. of Vermont, Burlington, VT

Abstract: Mammals and insects alike depend on foodstuffs as an essential source of proteins and their constitutive amino acids, several of which cannot be synthesized by the organism. Amino acid (AA) consumption by *D. melanogaster* plays a crucial role in a variety of behaviors that impact the animal's survival and fitness, including feeding, mating, and egg laying. Underlying neural circuits that dictate such behaviors begin with the activation of distinct subsets of gustatory receptor neurons (GRNs) in the fly labellum that are divided into five types. However, the key GRNs and chemosensory receptors involved in the detection of AA ligands to elicit behavioral responses are not fully characterized. The present study employs behavioral paradigms with genetic tools to reveal the mechanisms of AA sensing on the labellum. We show that tryptone, a mixture of AAs, reliably induces the proboscis extension response (PER) in female flies and optogenetic silencing of each GRN type reveals three key cell types that contribute to the feeding initiation of AAs. Chronic silencing of each cell type to look at tryptone preference revealed similar and conflicting results to the PER, demonstrating that the role of some neurons is not conserved from feeding initiation to choice. Flies with mutations in candidate receptors indicate two broadly expressed co-receptors, IR25a and IR76b, along with two narrowly expressed receptors, IR51b and IR94e, are necessary for AA taste behaviors. In addition, sugar-sensing gustatory receptor mutants surprisingly showed opposite phenotypes for the PER and preference assay. This work improves our understanding of the complex, combinatorial mechanisms by which the nervous system encodes taste information to drive behavior. Future aims of this project will evaluate the modulation of AA taste detection and feeding by internal metabolic factors.

Disclosures: G. Davis: None. **M. Stanley:** None.

Poster

PSTR114: Taste

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.20/C105

Topic: F.01. Neuroethology

Support: NSF Award Number 2332375
University of Vermont Start Up Funding

Title: Ionotropic Receptor 94e modulates multiple behaviors that impact fitness in Drosophila melanogaster

Authors: *J. A. GUILLEMIN[1], M. STANLEY[2];
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Abstract: Chemosensory integration is essential for organismal fitness and success. In *Drosophila melanogaster*, the fruit fly, contact chemosensation occurs via sensory neural circuits to drive feeding, mating, and egg laying. Previous mapping of gustatory receptor neurons (GRNs) on the fly labellum, the primary tasting organ, identified a set of neurons in L-type sensilla defined by expression of Ionotropic Receptor 94e (IR94e), but the role of the *IR94e* receptor gene and the taste cells that express it remained unclear. To understand the GRNs behavioral output, we used optogenetics and chemogenetics to activate IR94e neurons and found that they drive mild suppression of feeding but enhanced egg laying. In vivo calcium imaging revealed that IR94e GRNs respond strongly to certain amino acids, including glutamate, and that *IR94e* is necessary and sufficient for this response. We find that removing the majority of the *IR94e* coding region in *D. melanogaster* through CRISPR/Cas9 gene editing produces several fitness-related phenotypes, including increased feeding on amino acids, decreased oviposition, and a decrease in longevity and starvation resistance. To contextualize these findings, investigation into natural variation in the form of single nucleotide polymorphisms within *IR94e* has shown correlation to fitness-related phenotypes like those found via the loss of the coding region. This implicates IR94e as a potential gene of large effect, which can impact the organism's fitness on multiple levels, via feeding, oviposition, and survival.

Disclosures: J.A. Guillemin: None. **M. Stanley:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.01/C106

Topic: D.05. Auditory and Vestibular Systems

Title: Can Ramped Pulses Improve the Discriminative Abilities of Auditory Cortex Neurons in an Animal Model of Cochlear Implant?

Authors: E. PARTOUCHE[1], V. ADENIS[1], C. HUETZ[1], ***J.-M. EDELINE**[2];
[1]Paris Saclay Inst. of Neurosci., Saclay, France; [2]Paris Saclay Inst. of Neurosci. NeuroPSI, Saclay, France

Abstract: For several decades, cochlear implant (CI) is the most successful neuro-prosthetic device allowing thousands of patients to recover hearing sensation and speech understanding. The performances are usually good in silence, but CI patients have more difficulties in the presence of background noise. Potentially, these limitations stem from the large spread of currents diffusing in the cochlea's perilymph when the different electrodes are activated. To

reduce this large spread of current, one potential strategy is to change the shape of the electrical pulses. In human, studies have used asymmetric rectangular pulses (Macherey et al., 2006, 2008). A new pulse shape, called ramped pulse, has been proposed (Ballestero et al., 2015) but only one study has showed that such pulses elicited eABR responses with lower thresholds and steeper growth functions than rectangular pulses (Navntoft et al 2020). Here, we report the consequences of using ramped pulses on the discriminative abilities of auditory cortex (ACx) neurons in anesthetized guinea pigs. The intracochlear stimulating array was a shortened version of the EVO electrode array used by Oticon Medical (Smørum, Denmark). It was composed of 6 ring-shaped Platinum-Iridium electrodes with a 0.0046mm² surface. Center-to-center inter-electrode distance was 600µm. Four shapes of ramped pulses were tested and 20 charge levels were used (3-31.5nC) to obtain the growth functions of ACx neurons. Recordings were collected by 16-channels electrodes composed of two rows of 8 electrodes separated by 1000 µm (350 µm between electrodes of the same row). Mutual Information (MI) was used as a metric to determine to what extent ACx neurons discriminate between the different charge levels.The four shapes of ramped pulses elicited cortical responses with (i) lower thresholds and (ii) higher maximal firing rates than the rectangular pulses, both with anodic and cathodic first phases. On average, the dynamic range was unchanged as the whole growth functions of most of ACx neurons were shifted toward lower injected charges. The MI values were computed for each recording (MI_{ind}) and also for the entire population of recordings (MI_{pop}) available with a given strategy (around 100 recordings). Based upon individual recordings, the mean MI values were similar between ramped and rectangular pulse shapes. However, based on the MI_{pop}, the ramped pulses led to higher discrimination abilities than the rectangular pulses, but only when the first phase was cathodic. These results suggest that ramped pulses can be considered as a good alternative to rectangular pulses, but the polarity of the first phase matters to benefit from this shape.

Disclosures: E. Partouche: None. **V. Adenis:** None. **C. Huetz:** None. **J. Edeline:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.02/C107

Topic: D.05. Auditory and Vestibular Systems

Support: Ministry of Youth Affairs and Sports, Government of India, Award ID: F.NO.K-15015/42/2018/SP-V
NBRC Flagship program, Department of Biotechnology, Government of India, Award ID: BT/MED-III/ NBRC/Flagship/Flagship2019
NBRC Core funds

Title: Hemispheric specialization of functions are tuned by conduction velocities of neuronal propagation in large-scale brain networks

Authors: *N. KUMAR[1], D. ROY[2,1], A. BANERJEE[1];
[1]Natl. Brain Res. Ctr., Manesar, India; [2]Indian Inst. of Technol., Jodhpur, India

Abstract: We propose a tuning-by-delay hypothesis to explain the hemispheric specialization of function that has intrigued psychologists, philosophers, neurologists and neuroscientists for decades. In the auditory domain, speech and melody processing are understood to be lateralized in the left and the right hemispheric brain areas, respectively. Thus, analogous to the notion of pleiotropy where one gene can influence two or three unrelated traits, there exists a shared structural connectome encompassing both hemispheres underlying speech and melody processing, which however gets segregated along left vs right hemispheres, respectively. Here, we demonstrate how empirical observations of hemispheric specialization of speech and melody are shaped by the computational time-scales of information integration in cortical networks. First, we demonstrate that context-specific causal outflow of information emerging from primary auditory cortices (PAC) drives the hemispheric specialization of speech and melody processing when human volunteers listened to a cappella songs placed within a delayed match to sample task while electroencephalogram (EEG) were recorded. Second, together with participant specific whole-brain connectome model guided by diffusion weighted imaging, we predicted individual specific lateralization indices of inflow in cortical sources - after rigorous source time series reconstruction of EEG spectra. High levels of accuracy in the prediction of laterality indices in the extended large-scale auditory related regions can be achieved after optimizing conduction speeds of information propagation over a neuro-oscillatory network - a novel way to interpret about the neural mechanisms. We demonstrate that parametric modulation of conduction speeds that effectively controls the transmission delays - a key metric for understanding information processing and control of any biological network. Thus, the transmission delay in turn, acts as the switch and triggered by the spectro-temporal complexity of the task context to select the geometry of lateralization.

Disclosures: N. Kumar: None. **D. Roy:** None. **A. Banerjee:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.03/C108

Topic: D.05. Auditory and Vestibular Systems

Title: Mathematical rules for computing spatiotemporal firing patterns of neural networks

Authors: *A. REYES;
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Abstract: In sensory systems, information about stimuli is represented via the diverse firing patterns and receptive fields of neurons. These response properties depend on the integration of excitatory and inhibitory synaptic inputs in individual neurons and on the subsequent interactions

between neurons in the active network. Here, the operations for combining the effects of excitatory and inhibitory inputs on the firing probability at the single cell and network levels are derived. A simple probabilistic model configured as a feedforward inhibitory circuit reproduces temporal firing profiles evoked in vivo with sensory stimuli (Fig. 1A, bottom: model-prediction; top: simulations with leaky-integrate-fire neurons). By adjusting the level of inhibition, monotonic and nonmonotonic rate level functions (B), multiplicative gain modulation (C), and input-output curves that are supralinear (sublinear) for weak (strong) inputs (B, inset) emerge. When formalized mathematically, the algebraic operations can be used to predict spatiotemporal firing patterns evoked in networks (Fig. 2). This general model, which reproduces many features of experimentally observed responses, bridges the gap between computations at the cellular and network levels.

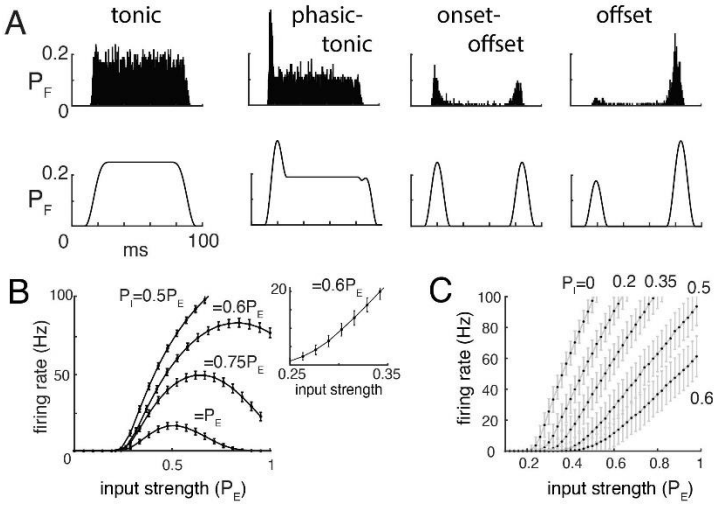

Figure 1: **A**, Temporal firing probability profiles (P_F) predicted by the model (bottom) and simulated with LIFs (top). The relative amplitudes and delays of inhibitory inputs were varied. **B**, firing rate vs input strength (excitatory probability, P_E) . Excitatory and inhibitory probabilities covaried as $P_I = kP_E$, $0 \le k \le 1$. Non-monotonic curves were obtained by increasing inhibition. **Inset**, blow up of curve with $P_I = 0.6P_E$. **C**, firing rate vs increasing input strength with fixed levels of inhibition ($0 \le P_I \le 1$).

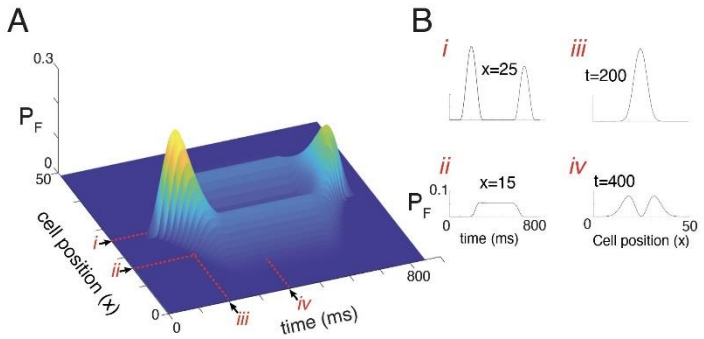

Figure 2: **A**, Example of spatiotemporal profile generated with model. The network is 1 dimensional (50 neurons). Excitatory and inhibitory input are Gaussian distributed in space, with inhibition 2x as broad. **B**, slices through surface along spatial (i,ii) and temporal (iii,iv) axes. Cells at center showed onset-off-set (i) responses while those towards the periphery were more tonic (ii). The spatial distribution was unimodal near the onset (iii) but bimodal midway through (iv).

Disclosures: A. Reyes: None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.04/C109

Topic: D.05. Auditory and Vestibular Systems

Support: NSF Grant IOS-1942480
NIH Grant DC018621-01

Title: Perceptual latent embeddings in local circuitry from an auditory illusion in zebra finches

Authors: *B. P. Q. LE[1], C. K. FEHRMAN[2], C. MELIZA[2];
[1]Psychology, Univ. of Virgina, Charlottesville, VA; [2]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: Perceptual illusions present an attractive problem in the study of neural systems: how do processing streams arise from neural activity that can, consciously or not, interpolate gaps in environmental input? Here, we focus on the illusory phenomenon known as auditory induction (or restoration), in which speech where syllables have been deleted and replaced with noise bursts is perceived as intact. Using single units recorded in vivo from the auditory cortex of anesthetized adult zebra finches, we show that even in the absence of top-down attention and explicit familiarity with the stimuli, the neurons responded to conspecific song with syllables deleted and replaced by noise as if the missing syllables were present alongside noise. This illusory response was absent when the stimuli comprised synthetic, lexically incoherent zebra finch songs, even after the birds were trained to recognize the synthetic songs in an operant task. These differences in illusory responses to natural and synthetic song motifs suggest that zebra finches have a consolidated internal model of conspecific song embodied in local neuron connectivity, which can serve as a template for auditory filling-in even without attention or top-down expectations. We employed dimensionality reduction techniques and a predictive modeling framework to explore the latent neural trajectories of the recorded population during presentation of induction-inducing stimuli. Our computational approach can help explain the perceptual processing strategies employed by the auditory cortex when sensory inputs are incomplete or corrupted by noise.

Disclosures: B.P.Q. Le: None. **C.K. Fehrman:** None. **C. Meliza:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.05/C110

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R00-DC015543
NIH Grant R01-DC021067

Title: Contributions and synaptic basis of diverse cortical neuron responses to flexible task performance

Authors: *X. ZENG[1], B. F. ALBANNA[2], M. INSANALLY[3];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Neurosci., [3]Otolaryngology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Flexible behaviors are critical for animals to adapt and survive in diverse and dynamic environments. However, the synaptic mechanisms that underlie flexible behaviors are largely unknown. Here, we combined in vivo electrophysiological recordings from mice performing a go/no-go auditory reversal learning task with a novel task-performing spiking recurrent neural network (RNN). Animals were trained to first respond to a target tone for water reward (i.e. pre-reversal) and withhold from responding to a non-target tone. Once animals reached expert levels of performance, we then implemented a rule switch and reversed which tone was rewarded (i.e. post-reversal) which required animals to remap stimulus-reward contingencies (d' = 1.87±0.21, N = 14 mice). We recorded single-unit responses from the auditory cortex of mice (n=1,327 cells) during all stages of reversal learning including pre-and-post reversal. We observed a wide range of single-unit response types from classically responsive cells that were highly modulated relative to pre-trial baseline to non-classically responsive cells with relatively unmodulated firing rates. To relate synaptic structure to spiking patterns over the response-type continuum, we developed a spiking RNN model incorporating both excitatory and inhibitory spike-timing-dependent plasticity trained to perform a similar go/no-go stimulus reversal learning task as behaving animals (d' = 3.72±0.31). This model captures the distribution of heterogeneous responses observed in the auditory cortex of behaving mice. We found that the level of inhibitory current was necessary for reversal learning. Specifically, this enhancement of inhibitory current was only required post-reversal for connections onto excitatory units. Furthermore, this resulted in an increase in the proportion of non-classically responsive units, recapitulating in vivo cortical dynamics observed during reversal learning in mice. Enhanced inhibition also increased network dimensionality by decreasing unit correlations, indicating a wider range of dynamic states capable of adapting to reversed task contingencies. These findings suggest that the level of inhibitory drive is a key factor in facilitating flexible behavior through expanded network dynamics.

Disclosures: X. Zeng: None. **B.F. Albanna:** None. **M. Insanally:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.06/C111

Topic: D.05. Auditory and Vestibular Systems

Title: Sex-specificity in encoding of two-tone harmonics in the mouse primary auditory cortex

Authors: *A. DE[1,2], R. ARCHAK[3,4], S. AGARWALLA[3,5], S. BANDYOPADHYAY[6,5];
[1]Advanced Technol. Develop. Ctr., Indian Inst. of Technol., Kharagpur, India; [2]Advanced

Technol. Develop. Ctr., [4]Dept. of Mechanical Engin., [5]Dept. of E&ECE, [3]Indian Inst. of Technol. Kharagpur, Kharagpur, India; [6]Dept. of E&ECE, IIT Kharagpur, Kharagpur, India

Abstract: Social communication among animals is crucial for their survival and mating. The optimum behavioral outcomes depend on a successful mechanism of transfer and perception of communication information between transmitter and receiver. Mouse, as a model organism, emits vocalizations, which are context-specific and with behavioral significance, like male's ultrasonic vocalizations (USVs) during courtship and mating and, pup isolation calls. Mouse vocalizations are enriched with harmonic syllables. Within these harmonic syllables, a significant proportion is two-tone harmonics (TTHCs). Our previous study reported that the mouse primary auditory cortex (Au1), is sensitive to vocalizations and synthetically designed TTHCs. This work is designed to decipher the possible differential encoding of two-tone harmonics between male and female mice based on their socio-behavioral roles with techniques like extracellular single-unit (SU) recording and 2P- Ca2+ imaging. SU responses from Au1 of anesthetized mice show that the distributions of best frequencies (BF) and best fundamental frequencies (BF0) from TTHC are different between males and females. It is observed that a large proportion of neurons have BF0s shifted by 1-octave below that neuron's BF. The above observation is true in females and not in males estimated from an octave shift measure (OSM). Thy1+ excitatory neuron populations probed with 2P-Ca2+ imaging show that their BF and BF0 distributions to be different in males as well as females. However, OSM at -1 octave is not significantly different. Parvalbumin (PV) and somatostatin (SOM) positive interneurons show no such sex-specific discrimination among BF and BF0. Types of TTHC response categories, namely enhanced (EN), suppressed (SP) and no-effect (NE) show that the proportion of single neuron responses is distributed differently from BF and BF0 in an octave scale. The response class proportions are indifferent among males and females, hence a unique feature of TTHC encoding. A sex-specific distinction of single neuron response in encoding TTHC is observed from pairwise noise correlation in Thy1 and PV neurons. Additionally, single-unit results indicate the ability of mouse Au1 to discriminate TTHCs from synthetic two-tone non-harmonic counterparts. The male-female distinction of non-harmonic encoding is visualized from normalized spike rates and EN, SP, and NE response cases distribution re-BF. Thus, this study reveals possible sex-specific single neuron mechanisms of encoding of TTHCs and non-harmonics.

Disclosures: A. De: None. **R. Archak:** None. **S. Agarwalla:** None. **S. Bandyopadhyay:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.07/C112

Topic: D.05. Auditory and Vestibular Systems

Title: Auditory cortex constructs noise-invariant representations of sounds in background noise

Authors: *T. SUAREZ OMEDAS[1], R. S. WILLIAMSON[2];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Otolaryngology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Discriminating relevant auditory signals from background noise (BN) poses a fundamental challenge to sensory systems. Primary auditory cortex (ACtx) plays a key role in disentangling auditory signals from BN by creating noise-invariant representations; however, the neural subpopulations and circuit computations that give rise to noise-invariance remain elusive. We studied how the sensory responses of three excitatory neuronal subpopulations, layer (L)2/3 intratelencephalic (IT), L5 IT and L5 extratelencephalic (ET), are involved in generating **noise-invariant representations**.We utilized two-photon calcium imaging in ACtx of awake, head-fixed mice to monitor each excitatory subpopulation during passive presentation of pure tones with/without a constant white BN. Using a combination of information-theoretic, manifold-geometric, and stimulus decoding analyses, we found that the presence of BN differentially modulated the responses of each ACtx subpopulation at both the single neuron and population level. In the presence of BN, L2/3 responses were largely suppressed, and the encoding of tones was less accurate. In contrast, L5 IT and ET each had similar responses with/without BN and encoded tones with similar accuracy.To relate this representational characterization to the underlying functional connectivity we designed a holographic optogenetics paradigm to excite groups of neurons that share similar modulation motifs and to quantify their influence on the rest of the neural population. We want to test the hypothesis that the influence of groups with similar modulation to motifs will have similar influence as groups of neurons that share sensory tuning curves. Taken together, these experiments show how noise-invariant representations are constructed across the cortical column.

Disclosures: T. Suarez Omedas: None. **R.S. Williamson:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.08/C113

Topic: D.05. Auditory and Vestibular Systems

Support: Wellcome Trust Grant WT108369/Z/2015/Z
University Of Oxford Medical Sciences Graudate School Studentship (covered partly by the Department of Physiology, Anatomy and Genetics and partly by the UKRI Medical Research Council)

Title: Gated recurrent models capture auditory cortical responses to natural sounds

Authors: *L. MAZZASCHI, A. J. KING, B. D. B. WILLMORE, N. S. HARPER;
Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

Abstract: Much of the activity of the brain that has been recorded in response to dynamic natural sounds, and consequently the processing that gives rise to it, remains to be explained.

Encoding models consisting of simple spectrotemporal filters and feedforward neural networks have had some success at predicting the responses of neurons in ferret auditory cortex to natural sounds. These include the spectrotemporal receptive field (STRF), the linear-nonlinear (LN) model, the network receptive field (NRF), and convolution-based neural networks. However, the proportion of the explainable variance in cortical responses to natural sounds that can be captured by the current best models is still under 50%. In addition, these models all require the use of unrealistically long delay lines to reach their best levels of prediction performance. We set out to improve on these models by introducing recurrent connections. Recurrency provides a form of memory, and, in principle, enables models to capture neural sensitivity to sequential dependencies, the latter being central to most natural sounds. Of particular interest to us was *gated* recurrency. Gates are sigmoidal functions that learn to recognize relevant information within memory and incoming data, controlling its flow through time. As a result, gated recurrent neural networks are well-suited for modeling long sequences. We explored two gated recurrent architectures, based on Long Short-Term Memory (LSTM) units and Gated Recurrent Units (GRU). We found that both of these network architectures offer better neural prediction performance in awake ferret primary auditory cortex than comparable feedforward neural networks, while also eliminating the latter's need for unrealistically long delay lines. Examination of the behavior of the gated recurrent models suggests some of the improvement they provide may be due to better capturing neural responses to silence. In particular, some neurons that benefit from the use of gated recurrency seem to be sensitive to the duration of periods of silence within natural sounds. We also found that some neurons were well-correlated with the activity of gates. Whether gating-like mechanisms actually exist in the brain, or the model gating approximates some other memory process, remains to be determined.

Disclosures: L. Mazzaschi: None. **A.J. King:** None. **B.D.B. Willmore:** None. **N.S. Harper:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.09/C114

Topic: D.05. Auditory and Vestibular Systems

Title: Temporal Encoding of Continuous Auditory Stimuli by Neuronal Populations in the Mouse Auditory Cortex

Authors: *Y. WANG, G. XIAO, J. WU, Q. DAI;
Tsinghua Univ., Beijing, China

Abstract: The auditory cortex is a crucial brain region for processing auditory information, distinguished by its diverse neuronal populations that decode sound features such as frequency, intensity, and temporal patterns. Despite extensive research, the mechanisms by which neural populations estimate the duration of continuous auditory stimuli, such as music, remain poorly

understood. To investigate the temporal information encoded by the auditory cortex, we employed large-scale in-vivo imaging (≥ 5 mm × 5 mm) and simultaneously recorded over 10,000 neurons in the auditory cortex of mice. We exposed mice to various types of continuous auditory stimuli, including music, pure tones, and noise. Following clustering and sorting of the neurons, we identified a subset (~10%) that selectively responded to the continuous auditory stimuli over durations of minutes. Projecting the population activity onto a two-dimensional embedding revealed a manifold resembling a sector, which encodes significant and reliable temporal information akin to an internal clock. These findings suggest that these neurons have the capability to encode information on a temporal scale, potentially playing crucial roles in the encoding, memory processes of continuous auditory stimuli, and the integration of multimodal sensory information.

Disclosures: Y. Wang: None. **G. Xiao:** None. **J. Wu:** None. **Q. Dai:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.10/C115

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01EB028155
NIH Grant R01DC014950

Title: Convolutional neural network models describe encoding subspaces of single neurons in auditory cortex

Authors: J. C. WINGERT[1], S. PARIDA[2], ***S. V. DAVID**[3];
[1]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [2]Oregon Hlth. and Sci. Univ., Portland, OR; [3]Otolaryngology, Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Understanding how the brain encodes and extracts information from dynamic natural sounds is a long-standing problem in sensory neuroscience. The classic linear-nonlinear spectro-temporal receptive field (LN STRF) describes encoding as convolution of the sound spectrogram with a linear spectro-temporal filter, followed by a static rectifying nonlinearity. Subspace encoding models have been proposed as a generalization of the LN STRF, in which the stimulus is convolved with two or more filters, and the response is then a nonlinear combination of the projection into this tuning subspace. Subspace models provide a logical, interpretable expansion of the LN STRF but have proven difficult to estimate accurately, especially for dynamic natural sounds. Recently, an alternative modeling framework, using convolutional neural network (CNNs), has proven effective at accounting for encoding properties in auditory cortex substantially better than the LN model. However, CNNs are complex and the functional properties that underlie their improved performance can be obscure.
The current study sought to measure the spectro-temporal tuning subspace from CNN model fits,

thus providing insight into their functional properties. Single-unit data was recorded using high channel-count microelectrode arrays from primary auditory cortex (A1) of awake, passively listening ferrets during presentation of a large natural sound set (45-90 min unique sounds). A CNN was fit to the data, replicating approaches from previous work. To measure the tuning subspace, the dynamic STRF was measured as the locally linear filter approximating the input-output relationship of the CNN at each timepoint in the stimulus. Principal component analysis was then used to reduce this very large number of filters to a smaller subspace. Typically, 2-10 filters accounted for 95% of variance in the dynamic STRFs. The stimulus was projected into the subspace for each neuron, and a new model was fit using only the projected values. On average, the subspace model was able to predict time-varying spike rate nearly as accurately as the full CNN. Sensory responses could also be plotted in this relatively small subspace, describing nonlinear tuning in this relatively compact space. This result indicates that the nonlinear encoding properties captured by the CNN can be described as a subspace encoding model, providing a conceptual link between these two modeling frameworks.

Disclosures: J.C. Wingert: None. **S. Parida:** None. **S.V. David:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.11/C116

Topic: D.05. Auditory and Vestibular Systems

Support: NIH - National Institute on Deafness and Other Communication Disorders - Grant R01 DC021140

Title: Testing candidate oscillatory models as explanations for the cortical tracking of natural speech.

Authors: *A. DURAN[1], A. R. NIDIFFER[2], E. C. LALOR[2];
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Abstract: Low-frequency cortical activity tracks the dynamics of natural speech. However, the field still lacks consensus regarding the precise physiological mechanisms of this tracking. One prominent model proposes that the quasi-rhythmic structure of speech entrains ongoing cortical oscillations, mediating the segmentation of sounds into phonetic-linguistic units (for example, phonemes or syllables). This falls in line with the widely accepted view that the brain extracts information from speech by passing neuronal representations of speech along hierarchically connected brain regions, each of which parses the speech at different timescales. However, the fact that cortical activity tracks the dynamics of speech is also compatible with an alternative model - one that assumes that such tracking reflects the summation of a series of transient evoked responses originating from neural networks tuned to various acoustic and linguistic features of speech. Here, we aim to compare these two potential explanatory mechanisms. In

particular, we begin by recognizing the fact that regressing neurophysiological data against the amplitude envelope of speech produces a temporal response function (TRF) which can reliably predict responses to novel speech stimuli. Then we ask the question: can candidate oscillatory models of speech tracking explain the existence speech generated TRFs? We do this by driving two oscillatory models with speech stimuli, attempting to fit TRFs to the resulting simulated brain activity, and then assessing whether the resulting TRFs can predict held-out simulated responses. One of the models is biologically implausible but produces reasonable TRFs, while the other produces simulated neural activity with atypical characteristics. We then extend our approach by modeling EEG datasets recorded while healthy, neurotypical adults listened naturalistic speech with modulated dynamic properties. Specifically, we model the EEG using the TRF framework (which is implicitly an evoked response model) and by fitting the abovementioned oscillator models using nonlinear optimization. This allows us to compare the temporal dynamics of the data simulated by each model against the dynamics of EEG. In addition, by determining oscillator model parameters via optimization to predict real EEG data, this work goes a step beyond prior studies using heuristically chosen parameters. This study establishes a framework for resolving an important debate in the field of speech - and indeed perceptual - neurophysiology.

Disclosures: A. Duran: None. **A.R. Nidiffer:** None. **E.C. Lalor:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.12/C117

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant U19NS112959
NIH Grant P30AG068635
NSF grant IIS-1724421

Title: Parsing the Temporal Hierarchical Structure of the Auditory Code

Authors: *H. ZHANG[1], I. NELKEN[2], T. O. SHARPEE[3];
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Abstract: There is a long-standing debate in neuroscience between the temporal and rate approaches for interpreting neuronal spike trains. The temporal approach argues that temporal patterns within neural spike trains carry different meaning beyond what can be deduced by measuring fluctuations in the instantaneous firing rate. The rate approach argues that, despite the large computational capacity that can be afforded by the temporal code, reading out this neural code will be too complicated. Therefore, the rate thesis states that only fluctuations in neural spike rate, perhaps on very short time scales, carry information. Currently this debate remains

unresolved with separate studies providing evidence for both the temporal and fast rate coding in the brain. Here we analyze multi-neural recordings in the auditory system to find evidence for a specific type of a temporal code that is easy to read-out and has a large computational capacity. Specifically, we find evidence for the so-called prefix-free code that has features of both rate and temporal approaches. The prefix-free code has a tree structure with partially pruned branches. The pruning is necessary to eliminate codewords that can be interpreted differently depending on how the spike trains are parsed. In particular, after pruning it becomes possible to interpret each codeword as soon as it has been produced, even though they have different durations. The prefix-free neural code has features from both rate and temporal approaches. On one hand, the codewords can be identified by the number of spikes they contain. On the other hand, because codewords with larger number of spikes take longer to produce, the neural code cannot be correctly interpreted by measuring the rate alone. Overall, these analyses indicate how the nervous system can achieve codes that are both efficient and easy to implement and interpret.

Disclosures: H. Zhang: None. **I. Nelken:** None. **T.O. Sharpee:** None.

Poster

PSTR115: Auditory Processing: Neural Coding, Experiment, and Theory

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Program #/Poster #: PSTR115.13/C118

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01EB028155
NIH Grant R21DC021048

Title: The cortical manifold for representation of natural soundscapes

Authors: *S. PARIDA[1], J. WINGERT[1], S. V. NORMAN-HAIGNERE[2], S. V. DAVID[3]; [1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Biostatistics & Neurosci., Univ. of Rochester, Rochester, NY; [3]OHRC, Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Neural manifolds (NM) provide compact, low-dimensional representations of heterogeneous, high-dimensional neural activity and can be used to relate neural circuit dynamics to sensory/motor coding as well as cognitive function. This functional relationship can generalize across subjects and across behavioral contexts within subjects, providing a general characterization of representation, independent of the specific neurons included in its measurement. The current study sought to characterize the NM for representation of natural sounds by single units in the auditory cortex.
We performed multichannel neurophysiological recordings from 1470 neurons in primary (A1) and secondary (PEG) fields of ferret auditory cortex. Data were collected during presentation of a large sound corpus comprised of two sets: 1) NM set (~100-s long), repeated for all neurons and used to identify the NM, 2) encoding model set (~10 hours), played cumulatively across recordings and used to train encoding models. The NM was estimated using PCA, and revealed

that a NM with only about 360 dimensions captures 80% of the variance for the entire neural population. Representational similarity analysis revealed that the NM was strongly correlated between estimations from different animals.
To gain an understanding of how sound is represented in the NM, we hypothesized that deep neural networks (DNN) trained to predict NM representations from auditory stimuli serve as a cortical encoding model. The encoding model can be used to thoroughly characterize the NM, such as the spectrotemporal tuning of its individual dimensions. DNNs with a wide range of architectures were trained to construct encoding models to optimize model hyperparameters. Preliminary results show a significant correlation between NM validation accuracy and neural PSTH prediction accuracy.
These results point to the existence of a general NM for auditory cortex, and suggest that this NM can be leveraged to train accurate auditory cortical encoding models. Future work includes: 1) comparing the accuracy of NM-based encoding models to that of other state-of-the-art encoding models and 2) employing subspace analysis to characterize spectrotemporal properties of the distinct NM dimensions.

Disclosures: S. Parida: None. **J. Wingert:** None. **S.V. Norman-Haignere:** None. **S.V. David:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.01/C119

Topic: D.06. Vision

Support: 1R21MH128601

Title: Do mice attend covertly? Non-invasive 3D gaze tracking during a touchscreen-based selective visuospatial attention task in freely behaving mice

Authors: *N. B. KOTHARI[1], S. B. MYSORE[2];
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Abstract: Humans and non-human primates can selectively process important stimuli in their environment using not only overt but also covert attention strategies. Covert attention imbues animals with the power to camouflage the direction of their gaze and to plan behavior without revealing intended actions. Recent work in mice has now established rigorous behavioral tasks to study selective spatial attention both in head-fixed mice (by others) and in freely moving mice (by us). However, whether mice attend covertly to stimuli for spatial decisions is largely unclear, and especially, whether they do so during naturalistic (unrestrained) engagement with the environment is unknown. Here, we developed a non-invasive technique for 3D tracking of task-relevant gaze movements in freely behaving mice engaged in our touchscreen-based task of

selective visuospatial attention and use it to address this question. Specifically, we trained mice on a touchscreen version of the classic flanker task of attention in humans, in which they learned to attend to information within a central visual target (vertical or horizontal grating), while ignoring information in a flanking distractor (also vertical or horizontal grating). We varied the relative priority between the flanker and target parametrically by keeping the contrast of the target constant and varying the contrast of the flanker (weaker to stronger than target's contrast). We found, consistent with previous results in humans and mice, that selective spatial attention can be consistently captured by a strong flanking distracter to maladaptively drive selection and behavior. Using synchronized cameras positioned around the touchscreen, 3D head-tracking, and eye-in-orbit tracking, we developed an approach to track the 3D gaze direction of mice during the task-relevant periods, i.e., periods in which they engaged with the touchscreen: the duration from trial initiation to stimulus presentation to attention and decision. This approach allows direct comparison of 3D gaze trajectories on trials in which attention is captured by the stronger *peripheral* flanker (i.e., in error trials) to those on trials in which mice attended to the *central* target stimulus (i.e., in correct trials). Our results suggest that mice can, and do, direct selective attention covertly to spatial locations, even during unrestrained (naturalistic) behavior.

Disclosures: N.B. Kothari: None. **S.B. Mysore:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.02/C120

Topic: D.06. Vision

Support: National Natural Science Foundation of China 32271060
Beijing Natural Science Foundation IS23073

Title: Feature-independent Encoding of Visual Saliency in the Mouse Superior Colliculus

Authors: *R. WU[1], J. XU[1], C. LI[1,2], Z. ZHAOJI[3,1], L.-Y. LI[4], Y.-T. LI[1];
[1]Chinese Inst. for Brain Res., Beijing, China; [2]Col. of Biol. Sci., China Agr. Univ., Beijing, China; [3]Col. of Chem. and Mol. Engin., Peking Univ., Beijing, China; [4]Capital Med. Univ., Beijing, China

Abstract: Detecting conspicuous stimuli in a visual scene is crucial for animal survival, yet it remains debated how the brain encodes visual saliency. Here we investigate how visual saliency is represented in the superficial superior colliculus (sSC) of awake mice using two-photon calcium imaging. We report on a feature-independent saliency map in the sSC. Specifically, conspicuous stimuli evoke stronger responses in both excitatory and inhibitory neurons compared to uniform stimuli, with similar encoding patterns observed in both neuron types. The largest response occurs when a salient stimulus is positioned at the receptive field center, with contextual effects extending ~40° away from the center. The response amplitude correlates well

with the saliency strength of stimuli and is not influenced by the orientation or motion direction preferences of neurons. Furthermore, visual saliency is encoded in a feature-independent manner, and neurons involved in saliency encoding are less likely to exhibit orientation or direction selectivity.

Keywords: visual saliency; feature-independent encoding; superior colliculus; awake mice; two-photon calcium imaging

Disclosures: R. Wu: None. **J. Xu:** None. **C. Li:** None. **Z. Zhaoji:** None. **L. Li:** None. **Y. Li:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Program #/Poster #: PSTR116.03/C121

Topic: D.06. Vision

Support: NIH R01EY005911

Title: Norepinephrine contributes to attention-related modulation of neuronal response gain in monkey superior colliculus

Authors: *S. GHOSH[1], J. H. MAUNSELL[2];
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Abstract: We have recently reported that norepinephrine (NE) plays a central role in driving spatially-selective improvements in perceptual sensitivity (*d'*) when monkeys do visual attention tasks (Ghosh and Maunsell, 2024). The superior colliculus (SC) receives dense NE innervation from the locus coeruleus, and several studies have shown that SC neurons are strongly modulated when animals attend to stimuli in their receptive fields. However, the precise contribution of SC to different aspects of attentional performance and the underlying neuronal mechanisms remain under debate. We trained rhesus monkeys to do a visual orientation-change detection task that directed their visual spatial attention to one of two locations in opposite visual hemifields. The monkeys reported whether the orientation of a test stimulus differed from that of a sample stimulus by making a saccade to one of two targets placed along a line orthogonal to the attended locations. Each monkey's behavioral *d'* was manipulated independently at two stimulus locations by adjusting the task difficulty. Decision/motor response criteria were held fixed. While the monkeys did the task, we recorded spikes from visuo-motor multiunits in the SC and unilaterally injected either clonidine (α-2 adrenergic agonist, 1 mM, 1.5 υl) or ACSF (1.5 υl) locally into the SC. Results from two animals showed that blocking of NE release in the SC using clonidine impaired perceptual detection (*d'*) of orientation changes in the visual hemifield contralateral to the injected SC, without affecting performance at the ipsilateral stimulus location (mean ± SEM change in behavioral *d'*: monkey S, contra, -1.2 ± 0.11, ipsi, 0.48 ± 0.26, N = 7 sessions; monkey P, contra, -0.59 ± 0.12, ipsi, -0.13 ± 0.15, N = 8 sessions; $p < 10^{-2}$, ANOVA).

Before injection, visuo-motor SC neurons (n = 47) in these animals showed strong modulation to visual stimuli when monkeys directed their attention to the contralateral visual hemifield location compared to the ipsilateral location. This modulation was reduced following clonidine injection (neuronal *d'*: before, 0.22, post-clonidine, 0.07, $p < 10^{-4}$; signed rank). The impact of clonidine on attention-related SC neuron response modulation (neuronal $d'_{clonidine}$- d'_{pre}) was correlated with the neurons' pre-injection response modulation (ρ = -0.86, $p < 10^{-6}$, Spearman correlation coefficient). Collectively, these results demonstrate that spatially selective improvements in perceptual sensitivity related with attention are associated with NE-mediated regulation of SC neuronal excitability.

Disclosures: S. Ghosh: None. **J.H. Maunsell:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

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Program #/Poster #: PSTR116.04/C122

Topic: D.06. Vision

Support: NIH Grant EY02966
NIH Grant EY035522

Title: Resolving the spatial scale of visuospatial attention effects in primate primary visual cortex.

Authors: *J. AMODEO[1], A. A. DISNEY[2];
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Abstract: Attention is central to how an observer squares loads of sensory information with computing a response on behaviorally relevant timescales, and its biological mechanism has long been an elusive target. Various neurophysiological effects of attention have been identified over the years, including increased gain and decreased correlated activity for sensory neurons sampling attended locations. Together, these have been argued to boost the ratio of activity encoding attended stimuli (signal) to all other activity in the population (noise). The power of local field potential gamma oscillations is also increased, reflecting greater local synchrony. This is posited to promote input summation in higher-order neurons. Several hypotheses about the biological basis of these effects have been proposed, such as glutamatergic feedback from prefrontal cortex—which is believed to operate on a fine spatial scale—and release of acetylcholine into sensory cortices by basal forebrain—which is assumed to operate on a wider spatial scale. One way to rule in or out candidate mechanisms that differ in spatial scale is to assess the spatial properties of visual attention's physiological correlates. We designed a peripherally cued four-choice direction-change-detection task intended to enable such measurements by controlling the locus of attention with respect to a recorded neuron's receptive

field. Here, we present data on the spatial scale of visuospatial attention in macaque V1 for one adult male rhesus monkey. This work is supported by NIH grants EY02966 and EY035522.

Disclosures: J. Amodeo: None. **A.A. Disney:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Support: NEI R001EY030200
NIH/Brain Initiative U19NS123717
NIDA R01DA050159
NIH/Brain Initiative R01NS122742

Title: Visual stimulation drives retinotopic acetylcholine release in the mouse visual cortex

Authors: S. G. KNUDSTRUP[1], C. MARTINEZ[2], B. RAUSCHER[2], P. DORAN[3], N. FOMIN-THUNEMANN[3], K. KILIÇ[4], J. JIANG[2], A. DEVOR[3], M. THUNEMANN[3], ***J. GAVORNIK**[2]; [1]Biol., Boston Univ., Allston, MA; [2]Boston Univ., Boston, MA; [3]Biomed. Engin., Boston Univ., Boston, MA; [4]BME, Boston Univ., Boston, MA

Abstract: Cholinergic signalling is involved in a variety of brain functions including learning and memory, attention, and behavioural state modulation but the spatiotemporal characteristics of neocortical acetylcholine (ACh) release are poorly understood. Anatomical studies of cholinergic projections arising from the basal forebrain (BF) show an overall lack of intra-region topographic organization on downstream targets such as primary visual cortex (V1), which is suggestive of diffuse and relatively non-specific spatial release patterns. (Colangelo et al., 2019; Muñoz & Rudy, 2014). The development of fluorescent ACh indicators (Jing et al., 2018) has made it possible to observe cholinergic how visual stimulation drives ACh release in visual areas with spatial and temporal precision. Here, we use mesoscopic imaging to show that visual stimulation drives ACh release patterns that conform to a retinotopic map of visual space in mouse V1. We recorded cholinergic activity in awake, head-fixed mice expressing the GRAB-ACh sensor (n=5, ages P60-P150). A subset of these mice (n=3) also expressed the calcium indicator jRGECO1a. The animals passively viewed visual stimuli while cortical activity was monitored using a custom-built four-color mesoscope capable of simultaneous measurement of cholinergic, hemodynamic, and calcium activity. During monocular visual stimulation, we found that GRAB-ACh fluorescence was localized to contralateral monocular V1 (V1m). Similarly, we found that a narrow stimulus that swept across the visual field drove cholinergic release specific to the stimulated region that was precisely aligned to the known retinotopic map across V1. This effect was observed in mice expressing the GRAB-ACh sensor alone and in those co-expressing jRGECO1a. This work demonstrates that sensory stimulation drives ACh released with far more

topographical specificity than previously assumed, suggesting new modes of functional cholinergic signalling in cortical circuits.

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Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Topic: D.06. Vision

Support: NSF CAREER 145241
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Klingenstein-Simons Fellowship Award in Neuroscience

Title: Optogenetic inactivation of macaque cortical area V4 during visual shape discrimination

Authors: Y. XIE[1], N. AGARWAL[2], *Y. EL-SHAMAYLEH[1];
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Abstract: Primates rely on visual shape information to identify and interact with objects in the world. Knowledge of how brain circuits process visual shape information is therefore essential for understanding how we perceive objects and how we subsequently act on them. Many neurons in macaque cortical area V4 are selective for visual shape, showing preferences for curved segments along an object's bounding contour. These neuronal responses are presumed to be a foundation for visual shape perception. However, little is known about how V4 activity is causally linked to perceptual judgments of object contours. We therefore assessed the effect of optogenetic inactivation of V4 on performance in a contour-based shape discrimination task. We trained macaques to perform a two-alternative forced choice discrimination task requiring fine-scale perceptual judgments of contour curvature. The animals viewed two comparison stimuli on a visual display and were asked to report the stimulus of higher contour curvature. To quantify behavioral performance, we varied the difference in contour curvature between comparison stimuli on each trial. On a random subset of trials, we used laser illumination to inactivate V4 neurons whose receptive fields overlapped one of the comparison stimuli. To facilitate the interpretation of results on discrimination trials, we also interleaved two types of catch trials: (i) detection trials requiring animals to saccade towards the stimulus; (ii) blank trials requiring animals to maintain central fixation. We hypothesize that inactivating V4 affects performance on discrimination trials but not on catch trials.
Preliminary data collected in one animal showed deficits in discrimination performance on laser trials compared to control trials. We quantified optogenetic effects on performance by fitting a logistic function to the psychometric curves obtained in each session. Optogenetic inactivation

resulted in shallower psychometric curves, consistent with higher perceptual thresholds. There was no change in performance on catch trials, suggesting that optogenetic inactivation did not impair stimulus detection or saccade execution, nor did it elicit detectable phosphenes in the receptive fields of transduced V4 neurons. We therefore attribute the deficits in discrimination performance on laser trials to an impairment in shape perception. These findings provide evidence for the causal role of V4 activity in perceptual judgements of contour curvature.

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Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Topic: D.06. Vision

Support: NIH Grant RO1-EY-016454
NIH Grant R01-EY-024662

Title: Wide dynamic range of neural responses in macaque V1 at single-cell and population scales

Authors: *H. YOSHIDA[1], Y. CHEN[2], W. S. GEISLER[2], E. SEIDEMANN[1];
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Abstract: What is the dynamic range of neural responses in the visual cortex as a function of stimulus contrast? The study of contrast response functions (CRFs) of neurons in primary visual cortex (V1) using grating stimuli has largely been limited to Weber contrasts up to 100%. However, patches with contrasts exceeding 100% are common in natural scenes and it is therefore important to characterize the dynamic range of individual neurons and neural populations in V1 over a wider range of contrasts. Here, we measured single- and multi-unit spiking activities using laminar probes (Plexon S-probe and Neuropixels probe) and widefield fluorescent calcium imaging signals from V1 of monkeys performing a fixation task where a small, white Gaussian stimulus was flashed for 200 ms over the range of 3-900% Weber contrast. To summarize the CRFs of each single- or multi-unit, we fitted the following nonlinear function to the responses of each unit:
$M_c = C / \sqrt{(C^2 + C_N^2)}$; $R_c = R_{max} \cdot Mc \wedge n_s$
where C_N is the normalization constant, n_s is the spiking nonlinearity exponent and R_{max} is the maximum response. V1 units display a wide-range of nonlinearities with a large fraction of neurons continuing to increase their response to contrast above 100%. We find a systematic relationship between C_N and n_s, where C_N decays approximately exponentially as a function of n_s. A small subset of the cells reach 90% of their R_{max} by 100% stimulus contrast (low C_N and high n_s) and the majority reach half of their R_{max} only at contrasts above 100% (high C_N and low

n_s).
We used widefield imaging to measure the GCaMP response from excitatory V1 neurons to the same Gaussian stimuli. Both the average unit response and the GCaMP response continued to increase monotonically above 100% contrast; however, the GCaMP response reached half of its maximal response at a higher contrast than the average unit response. Given our previous finding that widefield GCaMP signals are approximately linearly related to the locally pooled spiking activities of V1 neurons (Seidemann et al., *eLife*, 2016), our current results suggest that the neuronal pool contributing to the widefield calcium signal is likely biased towards neurons with high C_N and low n_s.
Overall, our results suggest that neurons in V1 have a wide dynamic range well beyond what has typically been studied in the literature, consistent with our previous finding that direct optogenetic stimulation in V1 can drive its population responses to levels much higher than 100% contrast visual stimulus (Chen et al., *eLife*, 2022). Therefore, to understand vision under more natural conditions, it is important to examine neural responses to stimuli within this wider range of stimulus contrasts.

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Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

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Program #/Poster #: PSTR116.08/C126

Topic: D.06. Vision

Support: RF1NS132288
R01NS109978
F31EY033691

Title: Standardized methods for training mice in a visual perceptual task that probes spatial attention

Authors: *N. ALLEN, K. PEELMAN, J. ZHUANG, M. LÓPEZ-ESTEVA, A. D. LIEN, J. DEL ROSARIO, J. AHN, E. KIM, Y. YANG, B. HAIDER;
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Abstract: Complex tasks in head-fixed, behaving monkeys have proven essential for understanding the neural basis of perception, and its control by cognitive factors such as attention. Inspired by this approach, several labs have now developed bespoke tasks for head-fixed mice that elicit selective visual attention, paving the way for use of cell-type specific recording and stimulation techniques to dissect the underlying mechanisms. However, it remains important to establish standardized, rigorous, high-yield protocols for behavioral training of mice, so that measurable effects of attention are repeatable across subjects and labs. We previously developed a head-fixed visual detection task for stationary (non-locomoting) water-

restricted mice, where selective spatial attention was provoked by presenting the stimulus at a particular location for several consecutive trials; it then switched to another location without warning for the next block of consecutive trials, eliciting well-known behavioral and neural signatures of spatial attention (Speed et al., 2020; 2021). We have now optimized, operationalized, and validated the training protocol so that expert and non-expert trainers achieve repeatable metrics of attentional effects within and across mice. The key advances for replicability comprise gradual introduction of increasingly complex aspects of the task, and quantitative benchmarks for progress through each training stage. This includes incrementally shifting the position of the stimulus (static Gabor grating) from the central to peripheral visual field, and gradually shaping psychometric performance across stimulus contrasts, before presenting the stimuli in multiple locations of the visual field. Of 25 mice trained with the protocol, all showed clear psychometric performance and performed hundreds of trials per day (380 ± 120) with high accuracy ($\geq 75\%$). They simultaneously showed improvements of detection speed and accuracy across trials at each stimulus location, consistent with attentional effects. Training time to expert stage varied across mice (32 ± 15 days), but learning was 53% faster ($p=0.004$) compared to our prior study. Of the 12/25 mice with neural recordings during behavior, 11/12 showed attention effects on at least half of all recording days. Overall, we establish a standardized behavioral protocol to train mice in a psychometric visual spatial attention task and will share these methods with the community to enable other researchers to study the neural basis of selective visual spatial attention in a rigorous, replicable task across laboratories.

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Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Topic: D.06. Vision

Support: NIH Grant EY028811

Title: Task learning increases redundancy of V4 responses as expected by hierarchical inference, but has unexpected impact on Choice Probabilities

Authors: *A. PLETENEV, S. LIU, A. C. SNYDER, R. M. HAEFNER;
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Abstract: Two frameworks inform our understanding of the role of sensory neurons during perceptual decision-making: classical encoding/decoding models, and the Bayesian brain hypothesis, which assumes that sensory cortex integrates feedforward sensory evidence

(likelihood) with feedback from internal beliefs (prior). Both theories predict that learning increases Choice probabilities, but differ in their prediction for the change in 'information-limiting' correlations (ILCs, [Moreno-Bote et al. 2014]). While the encoding/decoding framework suggests a decrease as behavior improves, hierarchical inference predicts an increase in ILCs as a result of variable, task-related feedback [Lange & Haefner, 2022].
We trained two macaques on two orientation discrimination tasks each, while recording from V4 using Utah arrays. We found a consistent trend: ILCs increase, and information becomes more redundant over learning. This validates a critical prediction of hierarchical inference models, and is consistent with prior studies that found task-aligned structure of noise correlations in trained monkeys [Bondy et al., 2018]. Importantly, our results challenge the interpretation that a decrease in noise correlations during learning and attention is responsible for the observed change in behavioral performance [Ni et al. 2018]. Instead, our empirical findings and new analyses of a hierarchical inference model [Haefner et al., 2016] suggest that the increase in ILCs reflects a redistribution of task-related information via top-down signals, increasing redundancy in sensory responses, but not reducing input information [Kanitscheider et al., 2015].
Surprisingly, our Choice probability (CP) results were less consistent: in only one of two tasks (for both monkeys) did we find an increase over learning and significant CPs at the end of learning. Paradoxically, we also found CPs<0.5 for the other task in one monkey. At the same time, we saw a robust choice signal across monkeys and tasks that evolved with learning, but was broadly distributed across neurons regardless of their task relevance. These findings challenge both feedforward and hierarchical inference views of CP dynamics, and add to growing evidence that our understanding of the CP phenomenon remains incomplete [Goris et al, 2017; Park et al. 2014]. Interestingly, this discrepancy may have gone undetected in classic studies due to the common method of aligning the CP of each neuron with it's tuning preference. We suggest that differences between cortical layers, and between excitatory and inhibitory neurons, may resolve this discrepancy in the hierarchical inference framework.

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Poster

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Program #/Poster #: PSTR116.10/C128

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RF1NS132288

Title: Neural signatures of perceptual performance in mouse dorsal lateral geniculate nucleus

Authors: *K. PEELMAN, N. ALLEN, B. HAIDER;
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Abstract: Visual perceptual tasks paired with neural recordings have been instrumental for understanding the neural basis of perception, and its control by behavioral context. This approach has now been used in many studies of visual perception in mice, enabling high-throughput, high-density recordings to dissect the underlying circuits. Many of these studies show that successful detection of a stimulus can be influenced by contextual factors, including arousal, reward, and other non-sensory factors. Where these contextual effects arise first in the visual system, and how they propagate, remains unclear. In our previous work, we found that layer 4 of primary visual cortex showed key neural signatures of successful stimulus detection (Speed et al, 2019). Here, we tested if these effects are already present in dorsal lateral geniculate nucleus (dLGN). We trained mice in the same psychometric visual spatial detection task, and used Neuropixels probes to record neural populations in the dLGN. Mice were head-fixed, non-locomoting (stationary in a tube), and water-restricted for motivation. Stimuli (Gabor gratings at multiple contrasts) were presented in one of two locations in blocks of several consecutive trials. Mice reported stimulus detection by licking for a water reward, and showed clear psychometric performance during all recording sessions (n=43). When the stimulus appeared in a neuron's receptive field (RF), visually-evoked dLGN spiking was greater on trials of successful versus failed detection ($p = 0.0012$, n=93). The pre-stimulus spontaneous activity remained similar across these trials, but when the detected stimulus instead appeared outside of the RF, spontaneous activity was elevated specifically before trials of detection failure ($p = 0.0014$). Interestingly, dLGN activity was also strongly modulated by non-visual aspects of the task, such as reward. Together, these preliminary data suggest that behavioural outcome and contextual factors modulate dLGN. We are currently investigating how spatial context (whether the stimulus is inside or outside the neural RF) modulates dLGN activity, and if these effects of spatial context resemble those of spatial attention, as observed in V1 during this same task (Speed et al, 2020).

Disclosures: K. Peelman: None. **N. Allen:** None. **B. Haider:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.11/C129

Topic: D.06. Vision

Support: NIH R01 EY02966
NIH F31 EY035522

Title: A d' analysis of n-alternative forced choice responses with temporal uncertainty

Authors: J. M. AMODEO, *A. DISNEY;
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Abstract: The signal detection theory framework is well-developed for forced two-choice tasks (whether two-alternative or two-interval forced choice) in which a signal is simply present or absent in each choice. However, the extension of this framework to multi-choice tasks (choices greater than two) and to tasks in which the signal present/absent identity of a choice changes within a trial (e.g. change detection task) appears nontrivial. Here, we propose an approach to this more complex analysis. The challenge specifically arises in defining chance performance, as required for calculating sensitivity (d'), which is defined as the hit rate z-score ([mean(hit) - chance(hit)] / SD) minus the false alarm rate z-score ([mean(false alarm) - chance(false alarm)] / SD). We approach this challenge by defining chance performance as the product of the spatial probability (over 'n' stimuli) and the temporal probability (over a time window within which the to-be-detected change will occur) of a hit or false alarm, given random behavior. For example, in an uncued, four-alternative, forced choice change detection task, we use spatial probabilities of 0.25 (1 target / 4 total stimuli) and 0.75 (3 distractors / 4 total stimuli) for chance hit rate and chance false alarm rate calculations, respectively. We then multiply this spatial probability by a 'temporal probability', calculated in the following way:First, we define a 'hit window': begins 100 ms after the to-be detected change occurs and lasts for 400 ms (maximum allowed saccade latency + flight time) . Next, we calculate what proportion of the entire stimulus presentation period—beginning when the 4 alternatives appear, and ending after the response window—the 'hit window' comprises. The remainder of the stimulus presentation window is the 'false alarm window' and has an equivalent proportion calculation. So, chance(hit) = 0.25 * ('hit window / stimulus period), and chance(false alarm) = 0.75 * (false alarm window / stimulus period).

Disclosures: J.M. Amodeo: None. **A. Disney:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.12/C130

Topic: D.06. Vision

Title: Modeling the early visual pathway using machine learning

Authors: *L. G. SANCHEZ GIRALDO, N. P. LANNING;
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Abstract: Understanding the underlying principles the brain uses to make sense of visual information can serve as inspiration for the engineering of systems with the same remarkable feats. We propose a model of the early visual system based on machine learning that, by incorporating biologically inspired informational constraints, is able to learn features resembling those observed in retinal and primary visual cortical stages (V1). Most previous work has focused on models that either emulate retinal or V1 encoding, separately. One exception being a recent model based on convolutional neural networks (CNN) that focuses on anatomical constraints to explain the emergent representations of retina and V1 in vertebrates, but dismisses

previous observations made by other models about the importance of robustness to noise and coding efficiency. Here, we propose a model based on a fully-connected neural network that can learn retinal and V1 features in tandem. The model is trained to reconstruct patches from a large collection of natural images and is composed of two stages of processing where robustness to noise and coding efficiency are controlled by saturating the outputs of the first stage, injecting noise and limiting the number of units that can be active. When these constraints are imposed, the first stage of our model captures the behavior of retinal simple cells to center surround stimulus and in the second stage, the ability to respond to visual edges of V1 simple cells. We propose a measure called *orientedness* to quantitatively discern between retinal features and V1 features. For center surround features prevalent in the retinal stage, our measure of orientedness provide low values, whereas visual edges result in large orientedness values. When our model enforces robustness to noise and coding efficiency, the average chi square distance between the histograms of orientedness of the two stages of the model is 0.306 (+/- 0.0934), and when the model do not enforce these constrains the average distance is 0.048 (+/- 0.0381). Our findings support the hypothesis that information bottleneck principles that limit the flow of information between stages of processing are responsible for the representations that arise in retinal and V1 stages in vertebrates.

Disclosures: L.G. Sanchez Giraldo: None. **N.P. Lanning:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.13/C131

Topic: D.06. Vision

Support: PNC / Edith Trees

Title: Beyond Behavioral Relevance: Primate Superior Colliculus Retains Visual Event Features in an Attention Task

Authors: *Z. WANG[1], J. P. HERMAN[2];
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Abstract: Primate superior colliculus (SC) contributes to the control of both eye movements and covert attention. Inactivation of the intermediate and deep layers of the SC (SCi/d) causes saccadic and attentional deficits. Many SCi/d neurons are phasically activated for stimulus onsets, saccades, and subtle visual feature changes in attention tasks. The similarity of SCi/d responses across types of visual events and behavioral responses raises the question of how SC output contributes to distinct functions across diverse tasks. Does SC serve a unified role across visual events, behavioral responses, and tasks? Or does SC's contribution vary depending on the specific visual event, behavioral response, or cognitive task being performed? To address this, we recorded SCi/d neuronal population activity from two monkeys during a covert attention task.

Monkeys were rewarded for reporting cued visual events (a saturation or contrast change) by releasing their hold on a joystick. If an uncued change occurred or if no change occurred, monkeys were rewarded for withholding their response (maintaining the joystick hold). Central fixation was required throughout the stimulus presentation and report. We found that SCi/d encoded not only the behavioral relevance of visual events (cued / uncued / no change) but also the visual feature content, despite minimal feature tuning and identical behavioral responses. Behavioral relevance of saturation (71%, bootstrapped 95% confidence interval = [62%, 80%]) and contrast events (91%, [85%, 94%]) could be decoded at levels significantly above chance (33%) with a linear classifier. Using a novel dimensionality reduction method, we found SCi/d activity discriminating saturation and contrast events occupied "encoding subspaces" that overlapped only partially. Decoding accuracy for each event type was significantly lower in the other's subspace (-12%, 95% CI = [-7.6%, -17%]), but not in their own subspaces (-4%, [-7%, 1%]). This shows that SC activity includes feature-specific information in its encoding of the behavioral relevance of visual events. Our results suggest that SC does not discard visual feature information to represent a unified map of behavioral relevance. How this feature information might be used by downstream brain areas driving behavioral responses remains unclear. More broadly our results imply that SC's contribution to diverse functions may arise from a combination of conserved and functionally-specific components.

Disclosures: Z. Wang: None. **J.P. Herman:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.14/C132

Topic: D.06. Vision

Support: STI2030-Major Projects 2021ZD0200200

Title: Ensemble perception of size in macaques

Authors: Z. LIU[1], Y. XIN[1], T. YANG[1], G. ZHOU[2], ***N. LIU**[1];
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Abstract: Limited by the capacity of the visual system (e.g., attention and memory), processing each individual group member simultaneously is unlikely possible at a glance. However, due to the numerous similarities across a group of objects, summarizing statistical information about group properties (e.g., the average size of oranges in an orange tree) can significantly speed visual information processing. This phenomenon, known as "ensemble perception" or "ensemble coding," has been extensively observed in humans for various low-level (e.g., orientation) and mid-level visual features (e.g., size) and even extends to high-level visual features (e.g., emotional expression). While visual information also plays a crucial role in the daily lives of

non-human primates (NHPs), which share close evolutionary ties with humans, little is known about whether they possess the ensemble perception ability observed in humans. In the present study, we conducted a behavioral experiment to investigate the ensemble coding ability in macaques. Additionally, we employed functional magnetic resonance imaging (fMRI) to explore the underlying neural mechanisms. Our results demonstrate the presence of ensemble coding in macaques. Furthermore, the fMRI findings reveal that ensemble coding in macaques relies on distinct brain regions separate from those involved in encoding individual object information.

Disclosures: Z. Liu: None. **Y. Xin:** None. **T. Yang:** None. **G. Zhou:** None. **N. Liu:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

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Title: Correlated variability indicates theneural information that guides behavior

Authors: *R. SRINATH, A. M. NI, M. C. CZARNIK, M. R. COHEN;
Dept. of Neurobio. and Neurosci. Inst., Univ. of Chicago, Chicago, IL

Abstract: Somewhat paradoxically, improvements in perceptual performance (e.g. those associated with stimulus contrast, attention, learning, task switching, or arousal/motivation) are usually accompanied by decreases in the correlations between responses of sensory neurons to repeated presentations of the same stimulus. Indeed, we recently showed that this variability explains virtually all the choice-predictive signals in mid-level visual area V4 (Ni et al, 2018). These results are counterintuitive because in theory, neural populations can encode stimulus attributes without being corrupted by correlated variability. This is possible because correlated variability largely fluctuates along one axis in neural population space (akin to a single, linear combination of neurons, which we term the correlated variability axis).
We propose that correlated variability axis reflects the sensory information that is communicated out of, rather than encoded in, a population of sensory neurons. In this scenario, behaviorally relevant information is encoded in a way that aligns with, rather than avoids, the correlated variability axis. To test this hypothesis, we analyzed the relationships between correlated variability and the representations of relevant and irrelevant stimulus features, decisions, and motors plan across several data sets. We found that:

1) performance on a change detection task was significantly better when V4 population responses to the original and changed stimuli happened to align with the correlated variability axis,
2) in a curvature estimation task in which we dissociated stimulus features, perceptual judgments, and the eye movement necessary to communicate the decision, we found that the correlated variability axis was better aligned with representation of the saccade plan than other features, and
3) in a two alternative forced choice task in which monkeys alternated reporting stimulus shape or color, information about shape aligned better with the correlated variability axis when it was task-relevant than irrelevant.
These results directly contrast the predominant hypothesis that relevant representations would be aligned to avoid corruption by response variability. Instead, they suggest that analyzing the task variables aligned with correlated variability is a good way to identify the information used to guide behavior.

Disclosures: R. Srinath: None. **A.M. Ni:** None. **M.C. Czarnik:** None. **M.R. Cohen:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

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Topic: D.06. Vision

Support: NIH Grant 1K99EY034699

Title: Causal decorrelation of cortical network improves visual detection performance

Authors: *A. R. ANDREI[1], V. DRAGOI[2];
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Abstract: Decorrelation of cortical networks has long been hypothesized to be beneficial for stimulus encoding and associated with increased attentional states. However, to test the role of correlations directly for perceptual performance requires altering correlations without affecting firing rates or global brain states. Here, we utilize the observation that cortical networks spontaneously decorrelate hundreds of milliseconds after optogenetic activation of excitatory neurons, when firing rates have returned to baseline. Low contrast visual stimuli presented after the offset of optogenetic stimulation during this interval of reduced correlations evoke the same number of spikes as those on randomly interleaved control trials, but are reported with significantly greater accuracy by both animals and machine learning decoders. We report results from 2 macaques, and correlations measured across 4733 pairs of light-responsive neurons in primary visual cortex.

Disclosures: A.R. Andrei: None. **V. Dragoi:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

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Program #/Poster #: PSTR116.17/C135

Topic: D.06. Vision

Title: Navigating dual-task complexity: cognitive-motor interference modulates neural resources allocation

Authors: *L. BOVOLON[1], F. DI RUSSO[2], M. BERCHICCI[1,2];
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Abstract: Introduction and objectives: Motor activity’s impact on cognitive performance has been predominantly studied in isolated contexts. Yet, ecologically valid approaches (e.g., dual-task; DT) reveal concurrent cognitive-motor performance decrements, known as cognitive-motor interference (CMI). However, the neural underpinnings of CMI remain unclear. The primary aim of our study is to explore exercise-induced behavioral and psychophysiological changes during cognitive-motor DT. Methods: 16 healthy male participants performed a simple response task (SRT) under two conditions: at rest and during an incremental cycling test to exhaustion. Cycling began at a power output of 50W, increasing by 50W every 4 minutes. Continuous electroencephalography (EEG) was recorded alongside heart rate (HR), and subjective ratings of perceived exertion were collected at the end of each 4-minute intensity block. Exercise intensity zones were defined based on individualized percentages of maximal HR. Behavioral performance metrics (accuracy, response time, and intra-individual variability) were assessed, and visual-evoked potentials (VEP) were analyzed to explore neural responses. To maximize signal-to-noise ratio, only the initial 4 intensity blocks (i.e., 50W, 100W, 150W, 200W) were considered and compared with the rest condition. Results: Participants reported up to moderate-to-heavy perceived exertion, and HR zones indicated exercise engagement predominantly within moderate intensity thresholds. Faster RTs were shown during rest and at 200W compared to 50W, alongside heightened intra-individual behavioral variability observed at 50W compared to rest. Exercise intensity significantly influenced N1 and P3 latencies, as well as P2 amplitude. Additionally, under DT conditions, the P3 exhibited signs of suppression. Discussion and conclusions: Current data suggest that, following an initial decline in performance, exercise attenuates CMI on behavioral metrics. Furthermore, ERP data suggests that DT reduces feedback from extrastriate areas and conceals late perceptual processes linked to resource allocation. Present findings provide valuable insights for understanding DT dynamics and mitigating CMI-related challenges, thereby enhancing mobility outcomes in vulnerable populations.

Disclosures: L. Bovolon: None. **F. Di Russo:** None. **M. Berchicci:** None.

Poster

PSTR116: Visual and Spatial Attention: Circuits and Behavioral Responses

Location: MCP Hall A

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Program #/Poster #: PSTR116.18/C136

Topic: D.06. Vision

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T32NS091018
JHU start up funds (SPM)

Title: Use of the Quartet multi-region miniscope to measure visual encoding properties of neurons in the anterior cingulate cortex of head-fixed mice

Authors: *J. BEDKE[1], W.-K. YOU[2,3], H. ADWANIKAR[1], S. P. MYSORE[2];
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Abstract: Head-mounted microendoscopic (‘miniscope') calcium imaging is an effective technique for measuring the activity of large populations of genetically targeted neurons in freely moving animals. This technique has typically been limited by its applicability for imaging in a single region at a time. The ability to access neural activity in multiple areas in freely moving animals can facilitate the investigation of coordinated neural representations underlying behavior. The Quartet multi-region miniscope (Bruker) powerfully enables imaging in up to 4 regions simultaneously. However, published studies have not yet reported the use of this tool. Here, as a first step, we report successful neuronal resolution calcium imaging with this multi-region miniscope in the primary visual cortex (V1) of head-fixed mice. We directly compare visual receptive fields obtained with the Quartet to those obtained with traditional extracellular electrophysiology to validate the measurement of visual responses of neurons with the Quartet. Building on this, we image visuospatial receptive fields in the anterior cingulate cortex (ACC) to characterize the hitherto unknown visual response properties of this higher-order area that is heavily implicated in visually-guided behavior. Our results open the door for future multi-region imaging in ACC and V1 using the Quartet in freely moving mice performing visuomotor tasks.

Disclosures: J. Bedke: None. **W. You:** None. **H. Adwanikar:** None. **S.P. Mysore:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

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Program #/Poster #: PSTR117.01/C137

Topic: D.08. Multisensory Integration

Support: PICT 2020-02136
PIP 11220200102799CO

Title: Auditory stimuli enhance visual responses in the optic tectum of zebrafish

Authors: *N. MARTORELL[1], E. MARACHLIAN[2], G. SUMBRE[2], V. MEDAN[1];
[1]IFIBYNE (UBA - CONICET), Buenos Aires, Argentina; [2]Biologie, École Normale Supérieure, Paris, France

Abstract: Multisensory integration is crucial to disambiguate the meaning of noisy stimuli, but how it is implemented at the neural level is still a topic of active research. The Optic Tectum (OT) in the zebrafish brain (Danio rerio) is known to be a visual processing hub. Neurons in the Tectal Neuropil (TN) are known to detect certain types of stimuli, like danger or prey stimuli (Barker and Baier, 2015). Neurons in the Periventricular Layer (PVL) relay this information to other regions, such as to decision-making neurons in the spinal cord (Zhu and Goodhill, 2023). We investigate if the OT responds to auditory stimulation, and whether the response to visual stimulation is enhanced by the addition of an auditory stimulus. 4-7 dpf transgenic zebrafish were embedded in agarose and recorded with a confocal microscope (transgenic line for a cytosolic calcium indicator, HuC:GCaMP6f, N=73) or with a Single Plane Illumination Microscope (nuclear calcium indicator, H2B:GCaMP6f, N=10). Five repetitions of visual looming stimuli and short auditory stimuli were presented either separately or combined. We designed high and low salience stimuli for both modalities by varying visual contrast and sound amplitude. Crucially, auditory responses were observed in the OT in 64% of fish and were stronger and more common in the TN than in the PVL. Responsive TNs showed a 200% increase in mean dF/F in auditory-evoked activity when compared to control trials. During multisensory trials, TNs showed an 18% increase in activation probability when compared to visual-only stimulation. This enhancement was only observed for the multisensory combination of lowest salience. This conforms to the principle of inverse effectiveness, stating that multisensory integration has a proportionally greater effect when signals are noisy or ambiguous. This study shows a classically visual brain region responding to a different modality. This highlights the integrative nature of the brain and opens the door to mechanistic studies which investigate the implementation of tectal integration and its effect on behavior.
Barker, A. J., & Baier, H. (2015). Sensorimotor decision making in the zebrafish tectum. Current Biology, 25(21), 2804-2814.
Zhu, S. I., & Goodhill, G. J. (2023). From perception to behavior: The neural circuits underlying prey hunting in larval zebrafish. Frontiers in Neural Circuits, 17, 1087993.

Disclosures: N. Martorell: None. **E. Marachlian:** None. **G. Sumbre:** None. **V. Medan:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.02/C138

Topic: D.08. Multisensory Integration

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Title: Excitatory and inhibitory neuronal types orchestrate circuit integration in the insular cortex

Authors: *Y. CHEN[1], B. C. JONGBLOETS[2,3,4], M. A. MUNIAK[1], I. K. GINGERICH[1], T. MAO[1];
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Abstract: The insular cortex (IC) is an information integration hub that mediates diverse functions such as decision making, taste perception, and interoception. These functions are conventionally attributed to topographic subregions along its anterior-posterior axis, with the anterior IC mediating cognitive functions and the posterior IC integrating sensory signals. Meanwhile, the IC also comprises three anatomical subregions roughly along its ventral-dorsal axis: the agranular, dysgranular, and granular IC (AI, DI, and GI), based on the absence, emergence, and full-presence of Layer IV. While great progress has been made to establish distinct functional roles of the anterior and posterior IC, it remains elusive as to what cellular and circuit mechanisms underline IC's functional diversity, and how such functional diversity is coordinated by the anatomically-defined AI, DI, and GI.
To address these questions, we first present a comprehensive atlas of IC pyramidal cell types, based on dendritic morphologies, intrinsic properties, and local connectivity from *ex vivo* whole-cell recordings of over 1000 neurons, mapped onto our Nissl-based IC reference framework that allows for the reconciliation of anatomical and functional subregions. We discovered cell types that preferentially localize to anatomically and functionally distinct subregions, project to specific targets, and receive unique local inputs. In particular, we identified cell types that receive excitatory intra-insular inputs that are distinct from canonical cortical microcircuits, and further demonstrated that these inputs might underlie long-sought circuits linking sensory information to valence.
Synergic with the excitatory pyramidal neurons, IC inhibitory neurons also play pivotal roles in circuit integration. Interestingly, parvalbumin (PV) neurons, often the most abundant inhibitory cells in neocortices, are much sparser in the AI than in the DI/GI. To further investigate the total excitatory and inhibitory (E-I) balance in AI and DI/GI, we coupled electrophysiology with laser-scanning photostimulation or targeted expression of Channelrhodopsin and discovered potential mechanisms for the AI to achieve comparable E-I balance to DI/GI subregions.
Together, our work identified cell types and circuit building blocks of the IC, and unraveled excitatory and inhibitory neuronal substrates orchestrating information integration that may contribute to its functional diversity.

Disclosures: Y. Chen: None. **B.C. Jongbloets:** None. **M.A. Muniak:** None. **I.K. Gingerich:** None. **T. Mao:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.03/C139

Topic: D.08. Multisensory Integration

Title: Embryonic exposure to Valproic Acid perturbs multisensory integration in the Xenopus laevis optic tectum

Authors: *C. A. TORO CEPEDA[1], Z. PEERBHOY[2], A. C. THOMPSON[2], C. D. AIZENMAN[3];
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Abstract: Impairments in social interaction and communicative abilities that characterize autism spectrum disorder (ASD) are thought to result from deficits in individuals' abilities to bind sensory cues from different modalities that are related and distinguish these from concurrent stimuli that are unrelated. Detection of amodal features of multisensory stimuli (ie synchrony or intensity) is imperative not only for understanding the prosodic elements of speech in humans, but also for the development of cohesive perception and selective attention that occurs in nearly all animals in order for them to successfully navigate their environments. Information from salient, unitary multisensory events is integrated in the CNS and relayed to motor output centers to elicit heightened behavioral responses through the process of multisensory integration. In this project we aimed to characterize early perceptual development in the optic tectum of the valproic acid-induced *Xenopus laevis* tadpole model of ASD. Specifically, we tested the effect of embryonic exposure to valproic acid (VPA) on tadpoles' ability to detect and respond to the temporal synchrony between visual and mechanosensory stimuli by presenting stimulus pairs across a range of time intervals and quantifying animal swimming behavior and cellular spike output. Using cell-attached patch clamp in an *ex-vivo* whole-brain preparation we found that VPA-exposed tectal neurons, as a population, were less selectively tuned to respond by enhancement or suppression to any given temporal window of multisensory stimuli as compared to typically-developing controls. These data correlated with differences observed in swimming velocity and overall motility of VPA-exposed and control tadpoles when presented with the same streams of multisensory information. Overall, these findings indicate potential developmental differences in brain wiring that lead to abnormal cellular and behavioral responses to multisensory stimuli, and may provide a mechanistic understanding of multisensory deficits seen in humans.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.04/C140

Topic: D.08. Multisensory Integration

Title: Digital Signature Library: using neurons as universal bio-digital sensors

Authors: *T. HONEGGER;
NETRI, Lyon, France

Abstract: Neurons process their inputs by either firing or remaining inactive, akin to generating binary signals of zeros and ones. Considering that every organ in the body is connected to nerves, the nervous system can be seen as a widespread network of bio-digital sensors. By linking neurons to specific organs, whether within the central nervous system (CNS) or the peripheral nervous system (PNS), we can encode the states of those organs (healthy, diseased, modified, etc.) into digital signatures. These signatures populate a Digital Library, establishing a framework for identifying and evaluating the effects of screened drug compounds based on desired functional outcomes. In our research across various studies and medical conditions, we employed NETRI's DuaLink MEA, DuaLink Shift MEA, and Trialink MEA compartmentalized chips along with Axion's Biosystems electrophysiology platform, Maestro. We connected different target organs "remotely" (such as skin, peripheral nervous system, and gut) to these chips and recorded their activity in both healthy and altered states. Using NETRI's UpLink software and the dedicated database DataLink, we extracted, processed, and analyzed the digital signatures of sensory neurons for each state with statistical significance. By defining digital signatures as an n-dimensional MEA-metric matrix representing proportional ratios between a reference state (healthy) and a target state (altered) across multiple repetitions, we were able to greatly mitigate the impact of individual cultural variations and demonstrate the quantification of drug candidate effects on a scale defined by reference compounds. Crucially, this was achieved non-destructively over acute or chronic timescales, without resorting to imaging or chemical assays. The primary concept emerging from this research is the standardized digitization capability facilitated by well-calibrated fluidically-isolated neuronal cultures for the analysis of organ function. Whether evaluating the effects of compounds on a disease, a topical cream on the skin, a nutrient in the gut, or guiding the repositioning of a drug, harnessing neurons as biodigital sensors offers a potent and adaptable platform solution across a broad spectrum of applications that extend beyond neuroscience.

Disclosures: T. Honegger: None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.08. Multisensory Integration

Support: NIH grant R01MH133181
NIH grant DP2MH132940-01

Title: High throughput corticothalamic projection mapping at single-cell resolution

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Abstract: Both cortex and thalamus are organized into specialized areas/nuclei, each with distinct connectivity and transcriptomic signatures. The precise connections between cortical areas and thalamic nuclei are essential for cognition, sensation, and motor coordination. Two distinct subclasses of cortical neurons, L5 extratelencephalic (L5 ET) and L6 corticothalamic (L6 CT) neurons, both project to the thalamus. Within each subclass, transcriptomically defined cell types at finer granularity are differentially enriched across cortical areas. However, it remains unclear whether these transcriptomically defined cell types can account for the distinct corticothalamic projections across cortical areas. Unraveling how transcriptomic identities of neurons contribute to differences in corticothalamic projections is challenging, because it requires interrogating both gene expression and long-range projections for many neurons with broad coverage across multiple cortical areas at cellular resolution. Here, we overcome these challenges using BARseq, a high-throughput neuroanatomical approach based on *in situ* sequencing. BARseq can reveal long-range axons of many neurons at cellular resolution by sequencing RNA barcodes that uniquely label individual neurons and their axons in situ. In preliminary experiments, we sequenced endogenous mRNAs and RNA barcodes from a continuous coronal section of mouse brain in which one hemisphere of cortex was tiled with barcoded sindbis virus. We found that the patterns of corticothalamic projections depend on both the transcritpomic identities and tangential locations of neurons. These corticothalamic projection maps are the first step towards understanding the transcriptomic logic of the cortico-thalamo-cortical loop.

Disclosures: M. Rue: None. **A. Zhang:** None. **L. French:** None. **A. Williford:** None. **B. Ouellette:** None. **C. Grasso:** None. **P.A. Groblewski:** None. **A. Oyama:** None. **A. Ayala:** None. **E. Liang:** None. **J. Ariza Torres:** None. **T. Egdorf:** None. **J. Gillis:** None. **X. Chen:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.06/C142

Topic: D.08. Multisensory Integration

Support: NIH Grant 1F32MH134455-01

Title: Multisensory processing in primate vestibular cortex: Vestibular and proprioceptive integration

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Abstract: Successfully navigating the environment requires perceiving both the orientation and movement of one's body in space. Fundamentally, these functions depend on integrating multiple streams of sensory input. For example, head-on-body movement generates both vestibular and proprioceptive input; when combined, these inputs provide context for both head movement and the relationship between body and head position. Integrating multisensory input is a function of many vestibular structures; however, integration at the neocortical level is thought to primarily underly self-motion perception. This idea is supported by the fact that all vestibular-sensitive areas of neocortex are inherently multimodal. Among these areas, the parieto-insular vestibular cortex (PIVC) is considered a principal vestibular processing area. Unlike other vestibular-sensitive areas, PIVC receives vestibular and proprioceptive input directly from the thalamus (as opposed to indirectly from other areas of cortex). Previously, integration of vestibular and proprioceptive input to PIVC has only been studied at the single-unit level, where no consistent integration scheme was found across neurons. However, we predicted that a more coherent integration scheme would be evident at the population level. Specifically, we hypothesized that integration in PIVC is accomplished by linear summation of vestibular and proprioceptive input at this level. To test this hypothesis, we investigated multisensory integration in PIVC by conducting high-density neural recordings in behaving non-human primates. Using Neuropixels electrodes, we characterized neural population responses to passively applied stimuli. We first tested vestibular sensitivity of PIVC neurons by applying whole-body yaw in the dark; we then tested proprioceptive sensitivity by applying body-under-head yaw in the dark. Consistent with previous findings, the majority of PIVC neurons were responsive to both vestibular and proprioceptive input. We then characterized the sensitivity of PIVC neurons to combined vestibular and proprioceptive input by applying head-on-body yaw in the dark. In preliminary results, the sensitivity of PIVC neurons to the combined stimulus was lower than that predicted by linear summation of vestibular and proprioceptive input; this result indicates that PIVC integrates vestibular and proprioceptive input sub-additively at the population level. Together, the results of this study will improve our understanding of sensory processing in PIVC and provide insight into the neural substrates underlying self-motion perception.

Disclosures: L.J. Gómez: None. **K.E. Cullen:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

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Program #/Poster #: PSTR117.07/C143

Topic: D.08. Multisensory Integration

Support: U01NS131438

Title: Multimodal integration of visual and mechanosensory cues for forward flight control in Drosophila

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Abstract: The ability to navigate through both familiar and novel environments is critical to an organism's ability to survive. The integration of information from multiple sensory modalities provides a robust and cohesive representation of the environment, enabling reliable production of motor commands for successful navigation. To better understand how the nervous system performs multimodal integration, we are investigating the flight control circuitry of the fruit fly, *Drosophila melanogaster*. The antennae of the fruit fly are a key site of mechanosensory input, processing air flow of the surrounding environment. This sensation is enabled by primary stretch-sensitive mechanoreceptors housed inside the antennae, known as Johnston's organ neurons. Mechanosensory information from these neurons is known to support several behaviors such as grooming, the startle response, and groundspeed regulation in flight. The compound eyes of the fly, meanwhile, process visual stimuli from the environment, and are crucial for many of these same behaviors. For instance, during forward flight, both progressive visual motion and airflow-induced antennal deflections contribute to the fly's sense of motion through the environment. Yet how information from these two sensors combine to guide ongoing behavior, particularly on the cellular and circuit level, is not well understood. We aim to probe this relationship by presenting wide-field visual motion and frontal airflow in both agreement and conflict (i.e. in same or opposing directions), while recording both antennal and wing movements. Through these experiments, we aim to understand the underlying integrative logic responsible for forward flight control. Furthermore, we are developing a control theoretical framework to create testable predictions for how this integration occurs at the cellular and circuit level. Together, this combination of control theory and quantitative behavioral analyses will advance our understanding of the process by which the brain processes salient multisensory information from the environment for regulating ongoing behavior.

Disclosures: K. Mills: None. **D. Biswas:** None. **N.J. Cowan:** None. **M.P. Suver:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.08/C144

Topic: D.08. Multisensory Integration

Support: P01NS074972
R01NS133751

Title: Distinct inhibitory and disinhibitory circuits mediated by neocortical VIP interneuron subtypes

Authors: *S. S. DELLAL[1], R. MACHOLD[2], I. KRUGLIKOV[4], H. ZURITA[3], J. H. MENG[5], B. RUDY[6];
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Abstract: GABAergic interneurons (INs) that express the neuropeptide vasoactive intestinal peptide (VIP) constitute a minority fraction of all INs in neocortex (~12% overall), but play a critical role in regulating local cortical circuit activity. In contrast to other GABAergic INs that mostly inhibit pyramidal neurons (PNs), VIP INs mainly target other INs - particularly the dendrite-targeting SST INs - thereby providing a major source of disinhibition in the neocortex. In sensory cortical areas (e.g., whisker barrel field cortex in S1 and primary visual cortex or V1), VIP INs are concentrated in superficial layers of the cortex and are the most abundant IN population in L2/3. VIP INs receive long-range inputs from corticocortical and thalamocortical projections as well as from subcortical neuromodulatory populations (e.g., cholinergic) that are active during arousal. Thus, via their disinhibitory role, VIP INs are critically positioned to enhance the responsiveness of PNs to top-down inputs from higher order brain regions during periods of exploration and learning. Consequently, VIP INs have been shown to regulate arousal, attention, and sensory processing. Furthermore, recent studies have linked impaired VIP IN function to schizophrenia and cognitive deficits associated with childhood epilepsy.
With the advent of molecular markers facilitated by single cell transcriptomic profiling, it is increasingly clear that VIP INs are a diverse population, yet the functional roles of distinct VIP IN subtypes and hence the significance of this diversity are not known. Here, we utilize intersectional genetic approaches to show that VIP INs consist of four distinct populations: two of these co-express the neuropeptide CCK, a third one co-expresses the Ca^{2+}-binding protein calretinin (CR) and the fourth expresses VIP but does not express CCK or CR. These populations differ in laminar distribution, morphology, in vivo activity and afferent and efferent connectivity, implying that they participate in distinct inhibitory and disinhibitory circuits. Our findings highlight the importance of understanding the differential connectivity and function of VIP IN subtypes in order to reveal the specific circuit mechanisms by which VIP INs regulate the dynamics of cortical activity, and how their dysfunction can contribute to cognitive impairment.

Disclosures: S.S. Dellal: None. **R. Machold:** None. **I. Kruglikov:** None. **H. Zurita:** None. **J.H. Meng:** None. **B. Rudy:** None.

Poster

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Topic: D.08. Multisensory Integration

Support: JSPS KAKENHI JP22J15034
JSPS KAKENHI JP20K07231
JSPS KAKENHI JP22K20694
JSPS KAKENHI JP22K15230
JSPS KAKENHI JP20K07743
JSPS KAKENHI JP21H02589
JSPS KAKENHI JP20H05628
JSPS KAKENHI JP21H02592
JSPS KAKENHI JP23K20044
AMED JP19dm0207093
AMED JP18dm0207020
AMED JP21dm0207112
JST JPMJMS2024
JST JPMJFR204D

Title: Subregional arborization patterns of parvalbumin- and somatostatin-positive GABAergic neurons in the mouse claustrum

Authors: *M. TAKAHASHI[1,2,3], T. KOBAYASHI[2,3], H. MIZUMA[2,3], S. OKAMOTO[2,3,4], K. YAMAUCHI[2,3], K. OKAMOTO[2,3], Y. ISHIDA[2,3,4], M. KOIKE[3], M. WATANABE[6], T. ISA[7,8], H. HIOKI[2,3,5];
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Abstract: The claustrum, a subcortical nucleus located between the insular cortex and striatum, consists of the core and shell subregions in mice. Although the claustrum coordinates the activities of individual cortical areas through abundant reciprocal connections with the cerebral cortex, the contribution of GABAergic neurons to the circuitry in each subregion remains to be elucidated. In the present study, we explored the distribution of GABAergic neurons and their dendritic and axonal arborizations in the claustral subregions of mice. Utilizing a combination of in situ hybridization and immunofluorescence histochemistry, we first investigated the distribution of neuronal nuclei (NeuN)-positive cells expressing glutamic acid decarboxylase 67 kDa isoform (GAD67) mRNA in each subregion. We showed that about 10% of NeuN-positive cells expressed GAD67 mRNA in both claustral core and shell regions. We also examined the proportion of parvalbumin (PV)-, somatostatin (SOM)-, or vasoactive intestinal polypeptide (VIP)-positive neurons in GAD67-expressing neurons and demonstrated that PV-, SOM-, or

VIP-positive neurons consisted of 20%, 30%, and 10%, respectively, of claustral GAD67-expressing neurons. Further, we selectively visualized PV or SOM- positive neurons by injecting recombinant adeno-associated virus vectors into the claustrum of PV- or SOM-Cre knock-in mice. We acquired the three-dimensional image stacks of optically cleared 1-mm-thick brain slices with a confocal microscope and reconstructed their dendrites and axons at the single-neuron level. Single neuronal reconstruction revealed that the dendrites and axons of PV- and SOM- positive neurons were preferentially localized to their respective subregions where their cell bodies were found. We also showed the axons were preferentially extended in a rostrocaudal direction, whereas the dendrites were relatively isotropic. These findings suggest that PV- and SOM-positive neurons preferentially localize the neurites to the claustral subregions, which might contribute to separate information processing within the subregions.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.10/C146

Topic: D.08. Multisensory Integration

Support: DP2MH122404-01
BRAIN RO1 NINDS
5T32NS126122-02

Title: An attentional set-shifting task with audio-visual stimuli for mice navigating in virtual reality

Authors: *A. BANDI[1], C. A. RUNYAN[2];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cognitive flexibility, the ability to adapt behavioral strategies, is essential for making choices in environments where stimulus and reward contingencies dynamically change. It is unclear how animals learn to make optimal navigational choices when current stimulus-choice-reward contingencies conflict with pre-existing contingences and previously relevant decision-making strategies. Furthermore, it is unknown how neuronal activity in cortical regions supports the recognition and resolution of conflict to enable cognitive flexibility. To study how animals learn to make flexible choices in multisensory environments with conflicting relationships between stimulus and reward, we developed a navigational set-shifting task with audio-visual stimuli. Mice are presented on each trial with one of two possible visual stimuli (25° vs. 65° orientation Gabor grating) and one of two possible auditory stimuli (pulse of sound from a speaker -90° vs 90° from the animal's midline) cueing them to turn left or right for a reward in a

virtual-reality T-maze. In alternating blocks, visual or auditory stimuli indicate the correct choice for a reward. In some trials, the audio-visual stimuli are congruent and indicate the same choice, regardless of the current block. In other trials, the stimuli are incongruent and have a conflicting stimulus-reward relationship, and so the mouse must use only the appropriate sensory modality to make the correct choice. Mice show near-perfect performance on congruent trials regardless of sensory rule block. Following a block switch, incongruent trial performance drops drastically below chance level, but mice learn the relevant sensory rule, perform even these difficult trials better than chance, and flexibly adapt to multiple audio-visual rule-switches in a single behavioral session. Modeling of the relationship between choice and various task features such as audio-visual stimulus information, sensory rule, and choice/outcome history, revealed that mice learn to make choices predominantly based on the relevant stimulus modality. With this task paradigm in place, optogenetic inactivation and two-photon calcium imaging can be used to explore the role of posterior parietal cortex, an association level cortical region involved in multisensory integration, in identifying conflict, and biasing sensorimotor responses during the period of choice formation to resolve conflict. In conclusion, we present a novel task paradigm that allows us to probe the relationships between flexible shifts in multimodal decision-making strategy and neural activity.

Disclosures: A. Bandi: None. **C.A. Runyan:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.08. Multisensory Integration

Support: T32 NS007433-22
DP2MH122404-01
BRAIN R01 NINDS
Mellon Fellowship

Title: Dynamic, context-dependent modulation of cell type-specific populations in the mouse posterior parietal cortex

Authors: *C. BASSI[1], C. A. RUNYAN[2];
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Abstract: Rapidly changing contexts can shift the meaning and importance of a sensory stimulus, yet the circuit-level basis behind this flexibly remains unknown. In this study, we explore the interplay between arousal and task engagement, variables known to modulate responses to incoming signals, and the neural circuitry within the posterior parietal cortex (PPC). We examine the role of inhibitory interneurons, known for their diverse connectivity and neuromodulatory receptor expression, in shaping sensory processing. We focus on two

prominent groups of inhibitory neurons distinguished by their molecular expression of parvalbumin (PV) or somatostatin (SOM) markers to elucidate their contributions to modulating responses to incoming auditory signals. Using two-photon calcium imaging, we simultaneously measured spike-related fluorescence changes in GCaMP6f of genetically identified PV and SOM neurons, along with putative excitatory neurons in mouse PPC layers 2/3. Within imaging sessions, mice experienced three distinct behavioral contexts: active engagement in a virtual reality-based sound-guided navigation task, passive exposure to the same sound stimuli, and spontaneous activity without sensory input. To probe the responsiveness of these neurons, we used ChrimsonR to optically stimulate incoming auditory axons. Optogenetic stimulations were timed to coincide with expected sound cues in active and passive contexts, while stimulation during the spontaneous context occurred at regular 10 second intervals. To quantify the impact of auditory axon photostimulation on individual neurons, we calculated a modulation index that reflects their responsiveness on average. Remarkably, we observed a decrease in modulation index during active engagement compared to passive or spontaneous contexts. Furthermore, putative excitatory neurons exhibiting high modulation displayed distinct activity dynamics across behavioral states, with some exhibiting anticipatory ramping activity preceding sound onset during active engagement. These findings highlight the dynamic and flexible nature of sensory processing within distinct neuronal populations in the PPC across varying behavioral states. By characterizing the contributions of PV, SOM, and putative excitatory neurons in shaping sensory responses, our study provides valuable insights into the neural mechanisms underlying flexibility in sensory processing.

Disclosures: C. Bassi: None. **C.A. Runyan:** None.

Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.08. Multisensory Integration

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NINDS RF1NS121913
Pew Biomedical Scholars Program
Klingenstein-Simons Fellowship Award

Title: Single-neuron-targeted stimulation reveals regional differences in local cortical network structure

Authors: J. MCCANN[1], C. F. KHOURY[1], *C. A. RUNYAN[2];
[1]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The general structure of cortical microcircuits is conserved throughout the cortical hierarchy; however, regional differences in the functional properties of this stereotyped

microcircuit could contribute to the variety of computations performed by areas throughout the sensory processing hierarchy. This study investigated local network influence of single excitatory neurons in layers 2/3 of primary auditory cortex (AC) and the posterior parietal cortex (PPC). We used an all-optical approach of single-cell-targeted optogenetic stimulation and 2-photon calcium imaging while the mice ran voluntarily on a spherical treadmill. Spike-related activity was monitored in all neurons by imaging fluorescence changes in virally expressed GCaMP6f. Optogenetic stimulation was mediated by targeting excitatory neurons expressing the red shifted excitatory opsin C1V1 with an independently scanning 1045 nm laser beam. Additionally, SOM inhibitory interneurons were transgenically labeled with tdTomato, in order to reveal potential differences between excitatory-excitatory and excitatory-SOM influence. Data from nine mice were included in this study with a total of 181 stimulation targets in AC and 278 in PPC. To statistically characterize the influence of the photostimulation on the neural population, we used generalized linear models (GLMs). The GLM approach allowed us to disentangle the influence of photostimulation and the mouse's running behavior on neural activity. The results revealed both cells that were positively and negatively influenced by the photostimulation, in both cortical regions. In positively influenced cells, there was a strong inverse relationship between magnitude of influence and distance from the stimulated neuron; however, the spatial spread of influence was broader in PPC than in AC. Furthermore, the spatial spread of positive influence was wider on SOM than non-SOM cells in both regions. These observed differences in spatial distribution of influence between regions could contribute to the different functional properties of AC, as a primary sensory region of cortex, and PPC, as an association-level region. Negative influence, however, had a broader spatial distribution of similar scale in both regions. In conclusion, we have compared the effects of single-neuron activation on local neural populations in auditory and parietal cortices, finding that the spatial spread of this influence depends both on cell type and brain region. Our results yield new insight into potential differences in local circuit organization that could underlie differences in the function of local circuits across the cortex.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

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Program #/Poster #: PSTR117.13/C149

Topic: D.08. Multisensory Integration

Support: BBSRC BB/T016639/1
Wellcome Trust 223144 & 219627/Z/19/Z1
The Gatsby Charitable Foundation GAT3755

Title: Separate auditory, visual and motor signals in mouse superior colliculus

Authors: *F. TAKÁCS, C. BIMBARD, G. BOOTH, M. A. ROBACHA, M. SHINN, T. SIT, K. Z. SOCHA, K. D. HARRIS, P. COEN, M. CARANDINI;
Univ. Col. London, London, United Kingdom

Abstract: Introduction. The superior colliculus (SC) contains visual, auditory, and motor maps that are thought to support audiovisual processing and sensory-driven orienting movements. Here we examine the role of the mouse SC in an audiovisual localization task. Do SC neurons carry all visual, auditory, and motor signals necessary for the task? Do these signals mix at the level of single neurons? Are these signals necessary for performing the task?
Methods. We trained 11 mice to indicate the location of checkerboard images and pink noise sound bursts presented at varying azimuths, alone or in combination. We recorded the responses of ~800 SC neurons during the task and during passive replay of task stimuli. We also recorded passive responses in a separate cohort of untrained mice (~1,700 SC neurons, 10 mice). In a third cohort, we used optogenetics to inactivate the SC unilaterally (N=9) and bilaterally (N=3) during the task.
Results. As expected, we observed neurons responding to visual stimuli in superficial layers, and to auditory stimuli in deeper layers (both in untrained and trained mice). However, neurons responding to both modalities were rare (<5%). SC neurons also carried motor signals related to instructed movements (choices) and to the uninstructed movements that were often evoked by auditory stimuli. Linear regression analysis indicated that different SC neurons carried signals related to visual stimuli, auditory stimuli, instructed movements, and uninstructed movements. Unilateral inactivation of the mouse SC promoted ipsiversive movements both during auditory and visual choices. Bilateral inactivation restored behavior. The effects of SC inactivation were captured by a drift diffusion model, where each side of the SC injects a constant bias to the sensory evidence.
Discussion. These results indicate that the mouse SC carries all visual, auditory, and motor signals necessary for an audiovisual localization task. However, these signals do not mix at the level of single neurons, and do not appear necessary to perform the task. Instead the role of SC in this task seems to be to bias the competing choice options so that a downstream region can make the ultimate decision.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Program #/Poster #: PSTR117.14/C150

Topic: D.08. Multisensory Integration

Support: MNESYS (PE0000006)
PRIN MUR 20207S3NB8 "ACT2"

Title: A neurocomputational model of multisensory integration in the spatiotemporal domain

Authors: E. DI ROSA, M. MONTI, *C. CUPPINI;
Univ. of Bologna, Bologna, Italy

Abstract: It is well known that the response of a multimodal neuron to a pair of spatiotemporally congruent audiovisual (AV) stimuli is significantly enhanced as compared to those evoked by either of the modality specific stimuli presented in isolation. In terms of behavior, receiving such a pair of stimuli means responding faster and more accurately. Predictably, the spatial and temporal disparity between audiovisual cues plays a pivotal role in determining the nature of the integrated response, as no enhancement often takes place when stimuli are far from each other in time or space. Plenty of studies can be found in the literature that either investigated the temporal factors sustaining AV integration or described the optimal conditions for such a combination in space. Informative as they can be, these works only offer a limited perspective on the understanding of these processes, as our everyday life is an ever-changing stream of stimuli whose spatial and temporal features constantly interact and cannot be easily separated. At present, little is known about the interaction of the spatial and temporal features of AV cues at the neural level, and even in empirical studies researchers often struggle with clearly distinguishing the respective contributions of spatial and temporal disparities on behavioral evidence. Here, taking advantage of the predictive power of modeling frameworks, we developed a unifying neurocomputational model to identify any changes in behavior caused by the interaction of the temporal and the spatial offsets in the delivery of AV stimuli. The model combines biologically inspired traits of previously proposed networks that handled separately temporal and spatial aspects of multisensory processes and successfully reproduces existing data from two types of behavioral experiments: (1) bisensory reaction time (RT) tasks, and (2) auditory spatial localization tasks. Further investigation on the mechanisms implemented in the network confirmed that modality switch effects (MSE) observed on AV RT tasks can be explained by cross-sensory inhibition, while additional sensitivity analyses upheld the centrality of cross-modal and intra-area connections in regulating spatial-oriented behavior. Finally, predictive simulations suggested that cross-sensory competition associated with temporal MSE in unisensory switch conditions gradually decreases as a function of AV spatial disparity. We will further validate the proposed model with newly collected experimental data, by analyzing the effect of increasing AV disparity on temporal detection and spatial localization performance in additional multisensory configurations.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.15/C151

Topic: D.08. Multisensory Integration

Support: NIH Training Grant T-32 for Purdue's Training Program in Auditory Neuroscience

Title: Multisensory Integration of natural and artificial sensation during navigation in freely moving mice

Authors: *S. J. SENNEKA[1], M. C. DADARLAT[2];
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Abstract: Our senses are how we react to changes in the world around us and the loss of one of these senses drastically impacts how we interact with our environment. Methods of electrically stimulating cortical and peripheral neural tissues can create a form of artificial sensation that has even started to restore a lost sense in devices such as the cochlear implant. Previous research has described the process of multisensory integration as an amplified neural response to two unimodal stimuli that are spatially and temporally correlated but if/how the brain integrates artificial sensation such as intracortical microstimulation (ICMS) with natural sensation is still not well understood. In order to develop sensory prostheses that rely on the electrical stimulation of neural tissue, it is critical that the brain can learn to integrate artificial sensation with natural sensation to continue providing a unified perception of the world. To further study the process of multisensory integration and integration of artificial and natural sensation, I have developed a behavioral training cage for a basic navigation task in which mice are trained to go to a specific region of their cage that can be indicated by visual stimuli, auditory stimuli, ICMS, and any combination of those 3 sensory modalities. Both auditory and ICMS stimuli operate under a closed-loop feedback system in which the parameters of the stimuli change in response to the mouse's heading angle and distance from the target. 3 mice were trained on task with combined audio-visual stimuli guiding them to the target and reached an 80% success rate in navigating to the target in under 20 seconds within 3-5 days. After subjects had mastered the task, they were tested with sole-auditory or sole-visual stimuli and still continued to perform at a high success rate for each unimodal condition. Basic statistics such as their success rate and average time taken to reach the target don't show a significant difference between the combined and unimodal paradigms. In future work, I plan to train mice on combined visual-ICMS, auditory-ICMS, and audio-visual-ICMS in order to gain insight into how learning of artificial sensation is affected by multi-modal training.

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Poster

PSTR117: Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.08. Multisensory Integration

Support: NRF-2021R1A2C3012159
IBS-R002-A2

Title: Learning contingency enhances the selectivity of cross-modal inhibition in the mouse parietal cortex

Authors: *I. CHOI[1], S.-H. LEE[2,1];
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Abstract: Animals benefit from multisensory information in their surroundings. Previous studies have shown that animals exhibit different behavioral responses to multisensory stimuli depending on the combination of modality-specific stimuli with distinct contingencies. However, it is unclear how learning the contingency of sensory stimuli shapes cortical circuits to evoke such behavioral responses. In this study, we investigated how learning affects inhibitory circuits in the sensory and associative cortex for multisensory processing. We trained mice with audiovisual Go/No-go discrimination tasks and measured neural activities of layer 2/3 neurons in the posterior parietal cortex (PPC) and primary visual cortex (V1) by *in vivo* two-photon calcium imaging. In the naive mice, PPC neurons exhibited a broad auditory-to-visual inhibition in all pairs of multisensory stimuli we tested. However, in the expert mice who learned the Go or No-go contingencies in different pairs of audiovisual stimuli, selective auditory-to-visual suppression emerged in the PPC only between pairs of incongruent audiovisual stimuli but not between the congruent stimuli. On the other hand, we did not find such selective inhibition in the V1. By targeted optogenetic activation of single neurons during *in vivo* calcium imaging using the two-photon microscope, we found the auditory-responsive parvalbumin-expressing (PV^+) neurons exert selective inhibition only in expert mice but not in naive mice. Collectively, our findings demonstrate that contingency learning across sensory modalities forms a selective cross-modal inhibitory circuit in the PPC, not in the V1, leading to neural competition occurring primarily in the PPC under audiovisual incongruency.

Disclosures: I. Choi: None. **S. Lee:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

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Topic: E.03. Basal Ganglia

Support: NIH 1 R01 NS125521
NIH 1 R56 MH110529

Title: Dopaminergic Control of Sensorimotor Behaviors in Zebrafish

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Abstract: Sensorimotor behaviors are essential for survival and shaped by modulation from neuropeptides and neurotransmitters. Dopamine (DA) shapes behavioral states, including motor behaviors initiated by stimuli received from upstream sensory neurons. Previous research from the Douglass lab has shown that dopaminergic neurons expressing tyrosine hydroxylase 2 (th2) in the hypothalamus play an important role in the initiation and modulation of motor behaviors in zebrafish. There are four anatomically distinct clusters of th2+ neurons within the hypothalamus, including the preoptic nucleus (PON), posterior tuberculum, intermediate hypothalamus, and caudal hypothalamus. Projection mapping of these neurons suggests that only the PON cluster projects onto unique sets of premotor spinal projection neurons (SPNs) and are active during distinct swimming behaviors, including routine swimming and defensive swimming. This finding, along with the finding that ablation of PON th2+ neurons significantly reduces swimming activity, suggests that dopaminergic neurons control sensorimotor behaviors. However, it is still unknown how PON th2+ neurons are able to drive diverse swimming behaviors. We hypothesize that there are distinct th2+ neurons within the PON that selectively fire onto specific SPNs to control these behaviors. To test this functional heterogeneity, we will quantify changes in DA activity using both in vivo DA and calcium two-photon imaging during distinct swimming behaviors. Using the fluorescent dopamine sensor GRABDA, the spatiotemporal dynamics of DA release from th2+ axons onto unique clusters of SPNs during unique swim behaviors will be determined. In parallel, neuronal activity of th2+ axonal projections will be quantified using the calcium indicator GCaMP8s under different motor behaviors. We predict that during routine swimming behaviors, only PON th2+ axons innervating the nucleus of the medial longitudinal fasciculus (nMLF) will show activity, while during defensive swims,th2+ axons innervating the nMLF as well as the Mauthner array will be recruited. With these experiments, we hope to resolve the mechanisms used by PON th2+ neurons to control downstream SPNs and further elucidate the role of DA in the modulation of motor behaviors.

Disclosures: M. Swall: None. **A. White:** None. **J. Barrios:** None. **A.D. Douglass:** None.

Poster

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Program #/Poster #: PSTR118.02/C154

Topic: E.03. Basal Ganglia

Support: Cerebral Palsy Alliance Research Foundation (PG02518)

Title: Dbs modulates the pattern of signal transmission and power of local activity in pallido-thalamic network

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Abstract: Deep brain stimulation (DBS) is a neuromodulation technique used for treatment of disorders, including dystonia. Stimulation of the internal globus pallidus (GPi) of basal ganglia or the subthalamic nucleus (STN) typically confers clinical benefit, although the specific mechanism of action is unknown. Previous studies of dystonic patients show abnormalities in low frequency activity in GPi and other motor sensory regions, such as STN, and nuclei of thalamus. We hypothesize that the DBS works in part by altering transmission of abnormal signals in low frequency bands between different brain regions, at the stimulation site (locally) and across deep brain regions (globally). In other words, we hypothesize that DBS modulates the abnormal projections onto thalamic motor subnuclei by changing the pattern of transmission in pallidothalamic network, due to local and global changes in deep brain regions low frequency power. To test this, we recorded intracranial signals from thirteen patients with dystonia, during 55, 85, 185, 250 Hz GPi and STN DBS and baseline activity (DBS-off). We performed a transfer function (TF) analysis which allowed us to make comparisons between the mean TF gains in low frequencies for each deep brain network pathway for the DBS-on and DBS-off conditions. To test whether the DBS effect on the TF gains were local or global, we performed the same analysis on the power spectra (PSD) of each region with and without the DBS. Furthermore, to evaluate the differences between the optimal versus non-optimal DBS settings for our patients, we analyzed the effect of clinically effective DBS on the PSDs and the TF gains and compared that with the effect of non-optimal DBS. Our results show that GPi and STN DBS effectively increases the TF gains from pallidum to motor subnuclei of thalamus in low frequency bands ($p < .01$). The results from the PSD analysis confirms that this increase is both local and global ($p < .01$). However, the results on the effect of stimulating clinically effective targets (with optimal DBS setting) showed a higher TF gain from GPi to thalamic nuclei compared to that of non-optimal DBS setting, in beta and gamma bands ($p < .05$). We confirmed this result by showing that, while stimulating with the clinically effective setting, the local increase in PSD is lower than the thalamic increase in the PSD compared to the other settings ($p < .01$). These results elicit a better understanding of the mechanism of DBS. This provides knowledge for the development of closed-loop DBS for controlling the intensity and pattern of stimulation and could also help to further the design of brain-computer interfaces and neurorehabilitation systems.

Disclosures: M. Kasiri: None. **J. Nataraj:** None. **T.D. Sanger:** None.

Poster

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Program #/Poster #: PSTR118.03/C155

Topic: E.03. Basal Ganglia

Support: RF1-AG060754

Title: Cortical acetylcholine response to deep brain stimulation of the sub-pallidal forebrain

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Abstract: Deep brain stimulation (DBS) is the direct electrical stimulation of neuronal tissue. Application of DBS to the basal forebrain is under consideration to improve executive function in several types of dementia. While there is preliminary data on positive treatment efficacy in the clinic, the underlying biological mechanisms of acetylcholine (ACh) release from the basal forebrain due to DBS are incompletely understood. We created a mouse preparation that applies DBS while using in vivo 2-photon fluorescent imaging to measure changes in ACh binding induced fluorescence. Electrodes were implanted in the subpallidal basal forebrain and an imaging window was implanted over the ipsilateral somatosensory cortex. Stimulation revealed increasing acetylcholine responses with higher frequencies and longer stimulation times as has been previously documented. The use of GACh-3.0 with 2-photon imaging was performed with the time resolution of hundreds of milliseconds. ACh levels return to baseline with an approximate half-life of 10s, longer than previously thought. With the application of donepezil, an acetylcholinesterase inhibitor, there was a dose-dependent increase in ACh levels during stimulation with no alteration in recovery kinetics. These data, coupled with the expression of acetylcholinesterase in cholinergic axon membranes, suggest that ACh escapes from the synapse into the interstitial space, and that diffusion back to the synapse where it can be hydrolyzed is the rate-limiting step in ACh recovery.

Disclosures: K. Shanazz: None. **J. Sword:** None. **S.A. Kirov:** None. **P.J. O'Herron:** None. **D.T. Blake:** None.

Poster

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Program #/Poster #: PSTR118.04/C156

Topic: E.03. Basal Ganglia

Support: NIH Grant K99/R00

Title: Dopamine guides vocal learning through reinforcement

Authors: *J. KASDIN[1,2], A. DUFFY[3], N. NADLER[1,2], A. RAHA[1,2], A. L. FAIRHALL[3], K. STACHENFELD[4,2], V. GADAGKAR[5];
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Abstract: Many of our motor skills like speaking or playing a musical instrument are acquired through a process of trial-and-error learning. It has long been hypothesized that dopamine plays a critical role in this process, motivated by two main findings. First, dopamine in the basal ganglia is thought to guide reward-based trial-and-error learning by encoding reward prediction error, decreasing after worse-than-predicted reward outcomes and increasing after better-than-predicted ones. Second, by changing the perceived song quality with distorted auditory feedback, our previous work in adult zebra finches showed that dopamine in Area X, the singing-related basal ganglia, encodes performance prediction error; dopamine is suppressed after worse-than-predicted (distorted syllables) and activated after better-than-predicted (undistorted syllables) performance. Here we parametrize developmental song learning trajectories in juvenile zebra finches into acoustic features and use fiber photometry to monitor concurrent dopamine activity in Area X. Dopamine was activated after syllable renditions that were closer to the eventual adult version of the song and suppressed after syllables that were farther away. Fitting the song trajectory to an actor-critic reinforcement learning model showed that dopamine corresponds to the prediction error term. The correlation structure between dopamine and song fluctuations revealed that dopamine activity attended to different song features over development and the direction in song feature space of maximal correlation with dopamine predicted the future movement of song. Reinforcement learning has contributed significantly to the current revolution in artificial intelligence. Our results show that complex natural behavior in biological systems can also be learned through dopamine-mediated reinforcement learning.

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Poster

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Program #/Poster #: PSTR118.05/C157

Topic: E.03. Basal Ganglia

Support: NIH/NINDS (R01 NS125143)

Title: Evaluation of DBS computational models using in-vivo electrophysiology in Parkinson's disease

Authors: *S. BORGHEAI[1], F. ISBAINE[3], E. OPRI[4], B. HOWELL[5], A. M. NOECKER[5], C. MCINTYRE[6], S. MIOCINOVIC[2,7];
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Abstract: The most common computational modeling methodologies to estimate deep brain stimulation (DBS) neural response are volume of tissue activation (VTA) and driving force (DF)

predictors. Despite their widespread use, a direct comparison of model accuracy with in-vivo electrophysiology is lacking. Our prior work evaluated the accuracy of DF models using cortical evoked potential (cEP) recorded intraoperatively in patients with Parkinson's disease (PD). Very short- (<2ms) and short-latency (2-3.5ms) cEPs have previously been demonstrated to reflect the degree of activation of the corticospinal/bulbar tract (CSBT) and the cortico-subthalamic hyperdirect pathway (HDP), respectively. The objective of this study was to compare the accuracy of VTA and DF models in predicting HDP and CSBT activations using in-vivo cEP measurements. The cEPs were previously recorded using temporary subdural electrocorticography strips in PD patients undergoing awake subthalamic (STN) DBS surgery. In each patient, cEP amplitudes were measured over the primary motor cortex. Lead locations for computational models were obtained from post-operative MRI. For DF models, we calculated percentages of pathway activation for CSBT and HDP defined by a connectomic atlas in patient (native) and Montreal Neurological Institute (MNI) atlas (normative) space. VTA modeling was conducted within the Lead-DBS toolbox (v3). The overlap of VTAs with internal capsule and motor STN structures were calculated as activation metrics for CSBT and HDP, respectively (VTA-structure) in both normative (MNI) and native spaces. Additionally, we calculated the percentage of fibers intersecting with Lead-DBS VTAs, defined by the same connectomic atlas used in the DF models, as alternative activation metrics in normalized space (VTA-pathway). The model performances were quantified using the coefficient of determination (R^2) between the cEP amplitudes and percent pathway activation or percent structure overlap. We compared model accuracy for 11 patients. The R^2 for HDP was 0.75 ± 0.15 for DF-native and significantly higher compared to 0.59 ± 0.20 for DF-normative, 0.42 ± 0.22 for VTA-normative-structure, and 0.39 ± 0.23 for VTA-normative-pathway modeling. For CSBT, the R^2 for DF-native modeling was 0.59 ± 0.29 and significantly higher compared to 0.40 ± 0.18 for DF-normative, 0.07 ± 0.10 for VTA-normative-structure and 0.27 ± 0.27 for VTA-normative-pathway. The DF models in native space more accurately predicted experimental subcortical pathway activations compared to the normative (VTA or DF) models. Our findings can help develop more accurate models to facilitate DBS clinical practice and research.

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Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

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Topic: E.03. Basal Ganglia

Support: This study was supported by National Natural Science Foundation of China (32130044 and T2241002, Y.S.)

Title: Asynchronous GABA release induced by deep brain stimulation desynchronizes subthalamic neurons and alleviates Parkinsonian motor deficits

Authors: *Z. XU[1], W. DUAN[2], S. YUAN[2], X. ZHANG[2], S. DENG[2], Y. SHU[2];
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Abstract: Deep brain stimulation (DBS) of subthalamic nucleus (STN) is an effective clinical therapy for Parkinson's disease (PD), but the underlying cellular and circuit mechanism remains unclear. The neural substrates affected by the DBS are complicated because the delivered electric pulses will non-specifically stimulate all tissues in the current path, including not only STN neurons but also traversing axons from other brain regions. In this study, combining local pharmacological application and STN DBS in dopamine-depleted (DD) C57 mice, we find a critical role of GABAergic transmission in the improvement of motor functions. In STN brain slices, high-frequency stimulation (HFS, up to 130 Hz similar to the therapeutic frequency) can evoke GABA release in both synchronous release (SR) and asynchronous release (AR) modes, resulting in an inhibition of STN neurons as well as a desynchronization of their spiking activity. In contrast, the AR with low-frequency stimulation (LFS, 20 Hz) is much weaker, suggesting that the strength of AR may determine the DBS therapeutic efficacy in intact animals. With optogenetic stimulation in brain slices, we identify the GABAergic resource inputs coming from the upstream external globus pallidus (GPe), including parvalbumin (PV) and non-PV neurons. In agreement with slice experiments, optogenetic stimulation of GPe-PV (but not non-PV) axons inhibits and desynchronizes STN neurons, and significantly improves the locomotion behavior in DD mice. An increase in AR strength by knocking down the calcium sensor synaptotagmin-1 in GPe PV neurons can significantly improve the DBS effect with both HFS and LFS. Together, our results show that the GABA release, especially its AR, from GPe-PV neurons, in response to HFS will inhibit and desynchronize STN neurons, leading to an improvement of the motor function in Parkinsonian conditions. Thus, these findings suggest a key but neglected mechanism underlying DBS for effective treatment of PD and even other neuropsychiatric disorders, and identify the AR as a potential biomarker for optimizing DBS parameters.

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Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

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Program #/Poster #: PSTR118.07/C159

Topic: E.03. Basal Ganglia

Title: Dips in dopamine concentration during voluntary, but not driven running are independent of subsequent reward

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Abstract: Dopamine in the dorsolateral striatum (DLS) is essential for movement, but its precise role in allowing, inhibiting, and reinforcing motor behaviors remains debated. In this study, we aimed to understand the dynamics of dopamine concentrations during the initiation and cessation of movements that were either linked or not linked with subsequent rewards. Because we found that mice did not run smoothly on driven treadmills for extended periods of time, we developed a task in which mice only ran with their front limbs, while their hindlimbs were supported by a platform. This allowed us to study the same behavior in a free and driven condition with extended temporal separation between initiation and cessation. We recorded DLS dopamine concentrations using the fluorescent dopamine indicator GRABDA3m. We found a remarkably consistent pattern of dopamine concentration dips as mice initiated running and bumps when they stopped - both for driven and voluntary running. To examine whether the dips and bumps of dopamine indicate the value of movement at those moments, we paired running initiation with subsequent reward. We found that this reward-pairing does not have a significant effect on dopamine dips for voluntary running, but the depth of the dip significantly decreased for driven running. These findings represent a counterexample to models in which dopamine motivates or reinforces movement at the moment of initiation and suggest that voluntary and driven movements differentially engage the dopamine system even in a simple behavior.

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Poster

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Topic: E.03. Basal Ganglia

Support: Intramural Research NIH

Title: Specialized Functions of Dopamine and GABAergic Neurons in the Dorsolateral and Ventromedial Substantia Nigra

Authors: *G. COSTELLO[1], R. J. KRAUZLIS[1], O. HIKOSAKA[2];
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Abstract: Midbrain dopamine (DA) plays a crucial role in reward-related learning by signaling reward-prediction errors. In addition, recent observations reveal increased phasic activity in DA neurons in response to non-rewarding sensory events and aversive stimuli, raising questions about the co-occurrence of phasic responses to aversion, reward, and movement in the same neurons or by different DA neuron groups. We conducted a comprehensive characterization of DA neurons within the dorsolateral and ventromedial substantia nigra pars compacta (SNc) using several behavioral tasks. Two principal subtypes of DA neurons emerged: 1) Salience-related DA neurons, which were responsive to both reward and aversion, exhibited long-term memory characteristics, pre-saccadic activity, and spatial selectivity and were mainly located in dorsolateral SNc, and 2) Value-related neurons, which were modulated by reward prediction errors, showed flexible responses, post-saccadic activity, and were primarily located in ventromedial SNc. The two types of DA neurons also differed in the timing of their discrimination between stimuli predicting good and bad outcomes, with salience-related neurons displaying earlier discrimination responses before the saccade. Furthermore, expanding upon these findings and our prior research, which suggested faster signal transmission through the Caudate tail-cdlSNr-Superior Colliculus (SC) circuit compared to the Caudate head-rostral ventral medial SNr-SC circuit, we explored the influence of the substantia nigra pars reticulata (SNr) on DA neurons. Our findings uncovered a subset of GABAergic neurons in the lateral SNr excited by aversive and non-rewarding stimuli that also had pre-saccadic activity for contraversive movements. This suggests a role for lateral SNr in disinhibiting DA salience neural responses to aversive stimuli, highlighting a potentially significant link between DA and GABAergic neurons in shaping behavior during learned aversive stimulus associations, where rapid alertness to potential threats is crucial. These results underscore an anatomical separation of two functionally distinct populations of DA neurons, with implications for understanding DA-related clinical conditions such as schizophrenia and Parkinson's disease. Reward-related DA neurons in medial SNc are implicated in cognitive functions, whereas the salience-related DA population are more closely linked to sensorimotor functions. These distinctions provide new insights into the circuit mechanisms underlying cognitive and sensorimotor dysfunction in DA-related disorders.

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Poster

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Support: NIH/NINDS R00 - 5R00NS107639-04
Michael J. Fox Foundation (MJFF) Aligning Science Across Parkinson's (ASAP) - ASAP-020519

Title: Characterization of dopamine signals associated with sensory versus motor processes in monkeys

Authors: *U. AMJAD[1], J. CHOI[1], S. MAHAJAN[1], O. COYNE[1], R. MURRAY[1], R. SHRIVASTAV[1], J. P. HERMAN[2], H. SCHWERDT[1];
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Abstract: The neuromodulator dopamine (DA) is most well known for its role in learning the reward value of stimuli and actions. However, DA also plays a key role in the generation of ongoing movements. When DA in the striatum is lost, as in Parkinson's disease in humans or in monkeys administered MPTP, motor function is severely compromised. Despite the clear relationship between DA signaling and movement, unambiguous dissociation of DA responses evoked by sensory versus motor events remains elusive. One limitation has been the lack of a task that temporally separates the presentation of sensory cues and associated motor responses. Here, we sought to distinguish DA signals related to sensory events versus those representing motor responses using chronically implanted electrochemical sensors that allowed us to sample dopamine release from multiple sites in the monkey striatum. We recorded subsecond DA concentration changes, using fast-scan cyclic voltammetry, from the striatum of a Rhesus monkey trained to perform a task where an image preceded the requested movement response by 2 s. This approach allowed us to better separate sensory and motor components of the recorded signals. Specifically, the task involved sensory deliberation and eye-movement responses to make a choice between two reward-associated "value images". Each value image was associated with a unique probability (0, 30, 70, or 100%) of reward (~ 0.15 ml of diluted apple juice). Given DA's central role in reward processing, we expected larger DA signals when higher value images were presented and/or selected. Each trial began with the display of a central circle that the monkey was required to fixate for 1 s prior to presentation of two value images which were presented concurrently next to the central circle for. During this "sensory deliberation period" (2 s), the monkey was required to maintain central fixation. At the conclusion of the sensory deliberation period, the central circle disappeared, indicating to the monkey that she should select one image by saccade and prolonged fixation (3 s) to receive the outcome: reward delivery or nothing. Initial analysis shows prominent DA concentration increases following movement in comparison to the initial presentation of the value images. These preliminary results support theories that motor actions, distinct from sensory cues, are capable of inducing DA release. We also measured DA signals modulated by image value and reward history, conforming to established reward prediction error functions. Ongoing analysis and data collection is underway to reproduce these findings and to further delineate DA signaling operations in multiple striatal sites and monkeys.

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Poster

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Topic: E.03. Basal Ganglia

Support: NIDA Grant DA000069

Title: Tracking synaptic Zn^{2+} and dopamine dynamics in the dorsal and ventral striatum of behaving mice

Authors: *O. SOLÍS CASTREJÓN[1], F. CURRY[1], H. ZHANG[2], Z. FRANGOS[1], W. HUANG[2], H. AI[2], M. MICHAELIDES[1];
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Abstract: The striatum integrates dopaminergic and glutamatergic inputs from the ventral tegmental area/substantia nigra pars compacta and the cortex, respectively. Dopamine in the striatum is critical for behaviors such as movement control, reward, and addiction. Striatal glutamate is critical for the modulation of synaptic plasticity and regulating the activity of striatal neurons. Importantly, a subset of cortical glutamatergic projections to the striatum corelease Zn^{2+}. However, the role of these projections in behavior is not well understood. Previous studies from our lab demonstrated that synaptic Zn^{2+} in the striatum modulates cocaine-induced behaviors and dopaminergic transmission. However, the changes in synaptic Zn^{2+} release and its relationship to dopamine release in the context of both normal behavior or behavioral effects of cocaine have not been studied. Here, we sought to draw parallels between dopamine and Zn^{2+} dynamics under three distinct conditions: animals in motion, immobilized states, and following an injection of cocaine. To test this, C57BL/6 mice were injected with a dopamine (AAV-hSyn-GRABDAm1) and/or a Zn^{2+} sensor (AAV-hSyn-GRISZ (green fluorescent indicator for synaptic Zn^{2+}) in the dorsal or the ventral striatum. Three weeks after AAV injection, we performed fiber photometry to record dopamine and synaptic Zn^{2+} dynamics during locomotion (mouse exceeded 5 cm/s), periods of immobility (below 0.25 cm/s) and following an injection of cocaine (10 mg/kg; i.p.). Our preliminary results showed that in the dorsal striatum, synaptic Zn^{2+} and dopamine release increased during locomotion and remained low when the mouse was immobile. In addition, when animals received cocaine there was an increase in dopamine and Zn^{2+} transient frequency. Synaptic Zn^{2+} transients were shorter in duration than dopamine transients. Our initial findings not only enhance our understanding of synaptic Zn^{2+}'s responsiveness to distinct behavioral states but also show our ability to detect and isolate phasic changes in striatal synaptic Zn^{2+}. Ongoing experiments are examining the dynamics of dopamine and Zn^{2+} in the ventral striatum.

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Poster

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Topic: E.03. Basal Ganglia

Support: T32NS007222

Title: Striatal dopamine and acetylcholine dynamics during skilled reaching

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Abstract: Striatal dopamine (DA) is essential for the production of intentional movements. Loss of striatal DA leads to slow movement, akinesia, and loss of coordination. Pharmacological replacement of tonic DA is sufficient to restore general movement, but not to rescue coordinated dexterous actions. Additionally, optogenetic stimulation of striatal DA release during a dexterous behavior (skilled reaching) only generates deficits in reach success and coordination in successive reaches, rather than immediately following stimulation. This indicates that striatal DA dynamics act as a learning signal that is necessary for executing and updating dexterous actions. Striatal acetylcholine (Ach) release, from cholinergic interneurons, is temporally linked to striatal DA release. Abnormal movements that result from alterations in DA signaling can be treated with anticholinergics, further strengthening the interdependence of these two systems in facilitating dexterous movements. However, the current body of work that focuses on striatal DA and Ach dynamics does so within the context of locomotion or other non-dexterous tasks. This leaves the manner in which striatal DA dynamics, striatal Ach dynamics, and their interactions support dexterous behavior unclear. We utilized two-color fiber photometry to simultaneously record DA and Ach dynamics in WT and dystonic rodents while they reached for sugar pellets (skilled reaching). Striatal DA and Ach dynamics were highly coherent both in response to external task events (ex. cue onset), reach sub-actions (ex. reach onset, grasp initiation), and pellet consumption. However, the precise timing of striatal DA and Ach dynamics was dependent on specific task events, with Ach peaks preceding or co-occurring with DA peaks during cue onset but following decreases in DA concentration during other task events. This suggests a context-dependent relationship between the two neurotransmitter systems which may serve to integrate relevant performance information.

Disclosures: A.T. Hodge: None. **M.A. Rasheed:** None. **C.R. Burgess:** None. **D.K. Leventhal:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.12/D4

Topic: E.03. Basal Ganglia

Support: ASAP 020600
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Title: Synaptic patterning of D1-receptor expressing dorsolateral striatal projection neurons by Aldh1a1+ and Anxa1+ substantia nigra dopaminergic neurons

Authors: *Y. LIU[1], M. DATUNASHVILI[2], A. LAHIRI[1], M. D. BEVAN[3];
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Abstract: Substantia nigra dopaminergic (DAergic) neuron subtypes exhibit distinct molecular, anatomical, and encoding properties. *Aldh1a1*-/*Anxa1*-expressing DAergic neurons in the ventral tier of SNc, innervate the dorsolateral striatum (DLS) and exhibit activity that is positively correlated with acceleration. These neurons are also more susceptible to degeneration in Parkinson's disease. In addition to the release of DA, SN DAergic neurons also co-transmit glutamate and GABA, although the underlying mechanisms, extent, targets, and functional impact are still being investigated. The aim of this project was to determine the impact of *Aldh1a1*+/*Anxa1*+ DAergic neuron transmission on D1 receptor-expressing striatal projection neurons (dSPNs) using optogenetic and electrophysiological interrogation approaches in *ex vivo* brain slices of DLS. Experiments were conducted using D1tdTomato, *Aldh1a1*-iCre or *Anxa1*-iCre mice in which AAV9 EF1a-DIO-hChR2(H134R)-EYFP-WPRE-HGHpA was injected into the SN. Amino acidergic transmission was assessed under whole-cell voltage clamp. Glutamatergic EPSCs were measured at -70 mV and GABAergic IPSCs were measured at 0 mV. Stimulation of *Aldh1a1*+ DAergic axons generated 75, 23-113 pA (median, interquartile range) EPSCs in all 38 dSPNs tested and 18, 0-40 pA IPSCs in 20 of 34 dSPNs tested. Stimulation of *Anxa1*+ DAergic axons generated 81, 49-104 pA EPSCs in all 33 dSPNs tested and 24, 0-75 pA IPSCs in 22 of 37 dSPNs tested. Occasional large IPSCs (100-650 pA were generated in 2/34 dSPNs (*Aldh1a1*+) and 6/37 dSPNs (*Anxa1*+) that were recorded in the most medial aspect of DLS that was sampled. To determine the impact of *Aldh1a1*+/*Anxa1*+ neuron amino acidergic and DAergic transmission on dSPN activity, recordings were made in the perforated patch configuration. Consistent with voltage clamp measurements, optogenetic stimulation generated time-locked EPSPs in 15 of 15 dSPNs, followed within a few a hundred milliseconds of stimulation onset by prolonged D1-receptor-dependent elevation of activity in 13 of 15 neurons. EPSPs were sensitive to pharmacological blockade of AMPA and NMDA receptors confirming their glutamatergic nature. Finally, the projections of glutamatergic DAergic SN DAergic neurons were visualized through the injection of AAV-DJ hSyn Con/Foff hChR2(H134R)-eYFP-WPRE into the SN of *Vglut2*-Cre/*DAT2A*-Flpo mice. These data confirmed that glutamatergic DAergic neurons project to the DLS, a subset of which are *Aldh1a1*-immunoreactive. Taken together these data argue *Aldh1a1*+/*Anxa1* acceleration-encoding DAergic neurons rapidly and persistently elevate DLS dSPN activity through the co-release of glutamate and DA.

Disclosures: Y. Liu: None. **M. Datunashvili:** None. **A. Lahiri:** None. **M.D. Bevan:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.13/D5

Topic: E.03. Basal Ganglia

Title: Ophthalmic Acid Acts as a Neurotransmitter with Motor Functions and Therapeutic Potential for Parkinson's Disease

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Abstract: Motor function regulation has long been attributed primarily to the actions of dopamine as the primary neurotransmitter. However, through our extensive investigations, we have made an exciting breakthrough by uncovering the involvement of ophthalmic acid (OA) as a previously unrecognized neurotransmitter with significant implications for motor function regulation. Our study began by challenging the traditional view of dopamine's exclusive role in motor function. We examined motor activity in mouse models of Parkinson's disease, conditions characterized by depleted dopamine levels. Our findings revealed robust and heightened motor activity when L-DOPA was administered alongside a central dopa decarboxylase (AADC) inhibitor, suggesting the involvement of non-dopaminergic systems. Interestingly, co-administering L-DOPA, a dopamine precursor, with an AADC inhibitor markedly increased brain levels of the tripeptide OA in these mice. To comprehensively understand the role of OA in motor function regulation, we conducted a series of behavioral, metabolomic, binding, and functional studies. Our results revealed OA as a potent mediator of motor activity through its activation of calcium-sensing receptor (CaSR) signaling. We established that OA is released from brain slices in a neurotransmitter manner, and it binds to CaSR in brain sections, exhibiting a high-affinity interaction. Furthermore, functional assays using cells expressing CaSR confirmed that OA activates CaSR-cAMP pathway in a dose-dependent manner, similar to the effects of the orthosteric agonist calcium ion (Ca2+). The identification of OA as a novel neurotransmitter regulating motor function has profound implications for our understanding of the complex mechanisms governing motor activity. It opens up new avenues for research and therapeutic interventions targeting the OA-CaSR pathway for movement disorders such as Parkinson's disease.

Disclosures: A. Alachkar: None. **O. Civelli:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

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Program #/Poster #: PSTR118.14/D6

Topic: E.03. Basal Ganglia

Support: City University of New York (CUNY) Interdisciplinary Research Grant (IRG)

Title: Angiotensin Converting Enzyme 2 (ACE2) activity modulates the physiology of cholinergic interneurons (CINs) of the striatum

Authors: *A. R. WALLS[1], L. J. LEE[2], L. S. MORGAN[2], A. H. KOTTMANN[3];
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Abstract: Brain-resident angiotensin converting enzyme 2 (brACE2) can participate in the production of peptidergic neuromodulators including endo-opioid, apelin, amyloid peptides, and peptides of the renin angiotensin system (RAS). Changes in the levels of ACE2-produced peptides have been observed in mental illnesses, suggesting the involvement of aberrant brACE2 activity. ACE2 is a peptidase expressed by neurons of the basal ganglia (BG). ACE2 activity is best known for processing angiotensin II (AngII) into angiotensin1-7 (Ang1-7) and as a result, can reduce physiological cell stress typically induced by activation of the AngII receptor AngII type 1 receptor (AT1R). Simultaneously, ACE2 actively promotes neurotrophic signaling by increasing Ang1-7-dependent activation of Mas receptors (MasR). While these observations suggest the possibility that virus-dependent inhibition of brACE2 could result in cognitive deficits observed in patients with “long covid”, the relevance of ACE2 expression and potential function in the intact brain remains controversial and ill-defined. Immunohistochemistry revealed that mesencephalic dopaminergic neurons (DAN) express ACE2 in a medial high to dorsal low gradient. Additionally, we find ACE2 protein expression in a medial high to lateral low gradient across coronal sections of the striatum. Further, we find prominent co-expression of AT1R and MasR on cholinergic interneurons (CINs) throughout the striatum suggesting that these neurons might be particularly sensitive to altered ACE2 activity. To determine whether ACE2 activity influences CIN physiology in vivo, we conducted pharmacological inhibition and genetic ablation studies in conjunction with fiber photometry (FP) using fluorescent sensors for dopamine (DA) and acetylcholine (ACh). Our experiments suggest that both, the local inhibition of ACE2 via infusion of the ACE2 antagonist MLN4760 or the acute ablation of ACE2 mediated by AAV-Cre expression at the recording site in the striatum, have profound effects on the dynamics of extracellular DA and ACh levels. Our FP analyses reveal that inhibition of ACE2 results in an attenuation of the characteristic “dip” or pause of CIN. These changes in the dynamics of extracellular ACh levels are associated with an increase in physiological cell stress levels in CIN. We are currently investigating the possibility of causality between the stimulation of the integrated stress response (ISR) in CIN by reduced Ang1-7 signaling as a result of ACE2 inhibition or ablation and changes in CIN responses to DA. We are also investigating behavioral consequences of local ACE2 modulation in the basal ganglia.

Disclosures: A.R. Walls: None. **L.J. Lee:** None. **L.S. Morgan:** None. **A.H. Kottmann:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.15/D7

Topic: E.03. Basal Ganglia

Support: CIHR PJT-183769-2022
Brain Canada Foundation - WBHI
Brain Canada Foundation - Future Leaders 2019

Title: Exploring the role of nucleus accumbense dopamine modulation in motor learning

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Abstract: Motor learning relies on reinforcement mechanisms driven by dopamine (DA) signaling. The nucleus accumbens (NAc), a pivotal structure within the basal ganglia, is renowned for its involvement in reinforcement learning via DA modulation. However, its specific role in motor learning remains underexplored. In this study, we aimed to elucidate how dynamic changes in dopamine modulation are influenced by various parameters of movement during motor learning processes. Using Long Evans rats, we unilaterally injected GrabDA, a dopamine sensor, into the NAc. Subsequently, rats were trained to execute a knob rotation task with an adaptive threshold using their right forepaw. We calculated success rate, rotation angle, speed, distance (rotation angle-Hit threshold) and confidence index (weight of past 3 trials) during the task, while concurrently tracking dopamine release dynamics via fiber photometry. Finally, we probed for correlations between behavioral and motor parameters and fluctuations in DA intensity and speed of change. Our findings unveil a multifaceted role of NAc dopamine release beyond its traditional association with reward processing and reward-predicting cues. We observed that dopamine release in the NAc not only encodes reward-related information but also reflects specific aspects of motor learning, contributing to the reinforcement of optimal movement patterns. This study sheds light on the intricate interplay between dopamine modulation in the NAc and motor learning processes, providing valuable insights into the neural mechanisms underlying skilled motor behavior.

Disclosures: Z. Vaziri: None. **M. Demers:** None. **S. Haj Azim Zanjani:** None. **C. Ethier:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.16/D8

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

Support: NIGS#T34GM145529
NINDS#1SC1NS119056
CORE NIH-N1MHD-RCMI#5G12MD007592
IDRB Imaging and Behavioral Neuroscience (IBN) Facility
NIH#C06OD030148

Title: Characterization of GlyT1-positive cells in the striatum

Authors: *I. A. GONZALEZ[1], M. A. YAGUE[2], L. P. MONTES[3], R. A. PEREZ[3], L. JIAO[4], M. MIRANDA-ARANGO[5];
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Abstract: Glycine is an inhibitory neurotransmitter present primarily in the spinal cord and caudal regions of the brain. The presence of glycine in the synaptic cleft is modulated by two transmembrane proteins, glycine transporter 1 (GlyT1) and glycine transporter 2 (GlyT2). However, the cells and neural circuits expressing these transporters have not been fully characterized. Therefore, the objective of this project is to characterize the phenotype of cells in the striatum expressing GlyT1. To do so, we used transgenic technology to identify the cell type and features of these cells. Immunohistochemical assays using neuronal nuclei (NeuN) and glial fibrillary acidic protein (GFAP) suggest the presence of glycinergic glia and neurons. These results suggest that in the striatum, there are different populations of cells that include GlyT1-positive neurons. Furthermore, the GlyT1-positive neurons display projections to regions involved in the basal ganglia circuitry. Overall, the significance of this data lies in a new population of putative glycinergic cells in the striatum that has not been described in the past.

Disclosures: I.A. Gonzalez: None. **M.A. Yague:** None. **L.P. Montes:** None. **R.A. Perez:** None. **L. Jiao:** None. **M. Miranda-Arango:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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

Support: NINDS 1SC1NS119056
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IDRB Imaging & Behavioral Neuroscience (IBN) facility NIH#

C06OD030148
LSAMP: HRD-1810898

Title: Blockage of strychnine glycine sensitive receptors in the caudate putamen and globus pallidus to test motor control in basal ganglia circuitry

Authors: *R. A. PEREZ[1], L. P. MONTES[2], V. GARCIA[3], K. S. PILLARO-ESTRADA[2], M. YAGUE[2], I. A. GONZALEZ[2], L. JIAO[2], E. CASTANEDA[3], M. MIRANDA-ARANGO[4]; [1]The Univ. of Texas at El Paso, El Paso, TX; [2]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; [3]Psychology, The Univ. of Texas at El Paso, El Paso, TX; [4]Dept. of Biol. Sci. and Border Biomed. Res. Ctr., The Univ. of Texas at El Paso, El Paso, TX

Abstract: Glycine is an inhibitory neurotransmitter predominantly found in caudal areas of the CNS that regulates autonomic functions. Two transmembrane proteins, glycine transporter 1 and 2 (GlyT1 & GlyT2) regulate glycine levels in the synaptic cleft. These transporters differ in location, while GlyT1 is widespread within the CNS and recognized as a glial marker, GlyT2 is secluded to caudal structures and expressed only in neurons. However, data from our lab suggest the expression of GlyT1 in neurons in the substantia nigra (SN); and more recently, anterograde adeno-associated viral particles (tdTomato flex AAV's) were injected in a rat knock-in-GlyT1-Cre line in the SN, revealing projections to the globus pallidus (GP) and caudate putamen (CP). In addition, the presence of glycine receptors (GlyRs) has been reported across the CNS, including forebrain and midbrain areas. Therefore, the objective of this study is to block GlyRs in the CP and GP to test basal ganglia-related functions. To do so, Sprague Dawley rats received intracranial infusions of vehicle or strychnine (glycine receptor antagonist), followed by an evaluation of motor behavior (open field locomotion), skilled limb use (ladder test), sensorimotor integration (sticky-dot), and postural reflex. The results support a potential contribution of glycinergic neurotransmission in modulating several aspects of motor activity. However, results are still preliminary as the number of subjects needs to be increased. Future directions include repetition of the experiment. Understanding the role of glycinergic neurotransmission in motor function control will provide a novel insight against motor disorders in addition to filling a gap of knowledge about GlyT1 phenotype expression, location, and function through the CNS since it is essential to better understand inhibition.

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Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: E.03. Basal Ganglia

Support: G-RISE T32GM136499
NIA 1R21 AG065682-0

Title: Characterization of striatal acetylcholine dynamics in vivo and the influence of sonic hedgehog signaling on cholinergic interneuron activity

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Abstract: A fundamental challenge faced by the nervous system is maintaining circuits that both rapidly learn stimulus-response associations yet retain enough flexibility to adapt when associations become obsolete. The striatum, a hub for learning in the brain, represents one such circuit. Specifically, midbrain Dopamine (DA) axons modulate striatal plasticity and promote the recurrence of DA-coincident behaviors. This pro-associative function of DA which strengthens synaptic connections calls into question what competing signals might act in parallel to maintain circuit adaptability. One major modulator of behavioral flexibility associated with striatal function is Acetylcholine (ACh). Specifically, the plasticity-promoting influence of DA seems to require low coincident ACh levels and local DA release can even be directly regulated by ACh via DA axon nicotinic receptors. Anatomically, Striatal Cholinergic Interneurons (CIN) are the major local source of ACh. Interestingly, these CIN exhibit a wide range of activation patterns, which include combinations of burst activity and preceding or subsequent hyperpolarization, the exact importance of which remains unclear. Additionally, while it is known CIN integrate numerous signaling pathways, some of which modify these complex activity patterns, the degree to which lesser-studied pathways contribute to these activity patterns remains unclear. Of particular interest are several peptidergic pathways CIN integrate which, by virtue of their relatively slower signaling speed, might act to modify rapid small-molecule signals preceding them. We previously observed that CIN are acutely responsive to changes in Sonic Hedgehog (Shh), a peptide released by DA neurons for which CIN are among the only neuronal recipients in the striatum. In the work presented here, we further probe the degree to which different patterns of ACh release in the striatum are dependent on Shh. Specifically, we utilize ACh and DA GRAB sensors to characterize ACh release patterns observed in vivo and associate them with aspects of locomotion and coincident DA signaling in animals with Shh pathway loss and gain of function mutations. Additionally, we highlight how diversity of locomotion and CIN activity elicited by optogenetic stimulation of DA neurons changes under different conditions of Shh pathway activation. Together, these results not only catalog the diversity of ACh signaling in the striatum, but also contribute to our understanding of how peptidergic signaling promotes this diversity and offers potential mechanisms by which the integrity of plastic striatal circuits might be maintained.

Disclosures: S. Uribe-Cano: None. **A.H. Kottmann:** None.

Poster

PSTR118: Basal Ganglia: Transmitters and Neuromodulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.19/D11

Topic: E.03. Basal Ganglia

Support: Parkinson's Foundation Impact Award
NINDS R01 NS135884

Title: Influence of estrous stage, nAChRs, and BDNF on exercise-enhanced dopamine release in female mice

Authors: R. M. FEELEY[1], J. C. PATEL[2], V. KHACHATURYAN[1], M. K. FERNANDES[1], B. GAMALLO-LANA[3], L. KHATRI[3], M. V. CHAO[4], A. C. MAR[5], ***M. RICE**[6];
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Abstract: Dopamine (DA) is an important modulator of movement, and loss of DA plays a pivotal role in the neurodegenerative motor disorder, Parkinson's disease (PD). Exercise has been shown to mitigate PD symptoms and has been used as an adjunct to DA replacement therapy for PD patients. Previously, using fast-scan cyclic voltammetry (FSCV), we found that 30 days of voluntary running-wheel-exercise leads to an increase in evoked extracellular DA concentration ($[DA]_o$) in striatal slices from young male mice compared to controls housed with fixed wheels (Bastioli et al. 2022). Amplification of evoked $[DA]_o$ in dorsal striatum (dStr) and in nucleus accumbens (NAc) in runners vs. controls persisted in the presence of a nicotinic acetylcholine receptor (nAChR) antagonist, DHβE, showing a cell-autonomous effect on DA axons. These increases also depended on brain-derived neurotrophic factor (BDNF), as no increases were seen in slices from runners that were heterozygous for BDNF deletion ($BDNF^{+/-}$). Here, we tested the hypothesis that voluntary exercise also boosts evoked DA release in the striatum of young (15-20-week-old) wild type (WT) female mice in a BDNF-dependent manner. As in young males, application of a TrkB agonists, LM22-A4 (1 μM), increased single-pulse evoked $[DA]_o$ in the dStr and NAc core compared to time-matched controls. Surprisingly, young females showed no obvious change in evoked $[DA]_o$ in any striatal subregion after voluntary exercise. This proved to be dependent on estrous stage. When runners and controls in estrus were compared, a significant increase in evoked $[DA]_o$ was seen in runners vs. controls; this was not seen in $BDNF^{+/-}$ mice in estrus. Suggesting estrous stage-dependent regulation by nAChRs, the difference between runners and controls was enhanced when nAChRs were antagonized using DHβE (1 μM). Additionally, previous studies have shown that hippocampal BDNF expression is highest during estrus. Using Western blots, we found that in all females, whether runners or controls, dStr BDNF levels were significantly higher during estrus than in non-estrus stages. Our results thus far support a DA-enhancing effect of exercise on striatal DA release in females, but that estrous cycle influence on striatal BDNF levels and possible nAChR-dependent regulation of axonal DA release add interesting complexity to the process.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.01/D12

Topic: E.04. Voluntary Movements

Support: COV-LT2-0022
MR/W004798/1

Title: Neurophysiological Measures of Central and Neuromuscular Dysfunction in Post-Covid Fatigue

Authors: *M. GERMANN[1], N. MAFFITT[2], O. BURTON[3], A. ASHHAD[3], A. BAKER[2], S. N. BAKER[2], D. S. SOTEROPOULOS[2], M. R. BAKER[3];
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Abstract: One of the major consequences of the COVID-19 pandemic has been the significant incidence of persistent fatigue following resolution of an acute infection (i.e. post-COVID fatigue). We have shown previously that, in comparison to healthy controls, those suffering from post-COVID fatigue exhibit changes in muscle physiology, cortical circuitry, and autonomic function.
Here we present results of a longitudinal study, comparing correlates of fatigue anywhere between 12 weeks and up to 45 months post COVID infection. All participants (N=145) were suffering from post-COVID fatigue at the time of testing. While post-COVID fatigue is defined as ongoing fatigue 12 weeks or more post COVID, many people do show significant recovery over time. However, others still have ongoing fatigue 2 years or more post COVID. This study aimed to investigate neurophysiological differences within this broad timeframe. We report self-perception of fatigue via questionnaires; as well as objective measures of cortical circuits via transcranial magnetic stimulation and reaction time tasks; peripheral muscle fatigue via twitch interpolation and nerve stimulation; and autonomic functions such as heart rate variability, oxygen saturation and body temperature. Additionally, daily activity levels were measured with a wrist worn accelerometer (Axivity) over a period of 14 days in a subset of participants (N=108).

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.02/D13

Topic: E.04. Voluntary Movements

Support: NIH Grant P41 EB018783 (Wolpaw)
NYS Spinal Cord Injury Research Board C37714GG (Gupta)
NYS Spinal Cord Injury Research Board C38338GG (Wolpaw)
Stratton Veterans Affairs Medical Center

Title: Reliability testing of EEG spectral features in a robot-based arm movement task

Authors: *S. RUEDA-PARRA[1], R. L. HARDESTY, Jr.[1], D. GEMOETS[2], J. HILL[1,3], D. GUPTA[1,3];
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Abstract: Introduction
We test the intersession reliability of kinematic and EEG low-beta (Lβ, 12 - 20 Hz) power features in a center-out motor task performed with the inMotion Arm rehabilitation robot from Bionik labs. Integrating EEG data collection with robotic tasks aims to reduce trial and session movement variability, and to obtain precise movement onset markers. We hypothesize that this setup would help reduce intersession variability and increase reliability, for potential use of these features in longitudinal assessments.
Methods
Ten right-handed healthy individuals used the Bionik robot in two sessions (on average 40 days apart) to perform planar movements within a predefined workspace. Targets were situated 10 cm from the center at 4 cardinal positions. Movement and targets were displayed on a screen. Movement was initiated upon visual cue and target position maintained till subsequent cue. Targets were presented randomly. Each arm performed a block of 80 movements, with randomized block order. Session two kept individual block order. Study was IRB approved (1584762); informed consent was obtained.
EEG data (DSI-24, Wearable Sensing) were collected at 300 Hz with BCI2000, referenced to linked earlobes, and synchronized with Bionik's positional data. Movement onsets were detected using inertial kinematic data with (Xsens, Movella). Lβ power was analyzed for epochs of 0 to 200 ms post-movement onset; expressed as a percentage change from trial baseline. Power distributions of this feature at contralateral hand motor regions (C3 and C4) were computed. Kinematic features (mean speed and movement duration) were gathered from the robot.
Inter session distribution differences were evaluated at individual (Lβ) and group levels (kinematics and Lβ). Wilcoxon rank sum test was used for intra-individual comparisons, and Wilcoxon signed rank for paired group comparisons. The group feature was the median Lβ power. Intersession agreement was quantified with the Inter-Class Correlation (ICC) coefficient.
Results
Lβ power in contralateral motor regions show expected desynchronization. Group analysis shows excellent agreement between sessions for right-arm (ICC: Lβ = 0.92, Speed = 0.86, Duration = 0.71), and left-arm (ICC: Lβ = 0.90, Speed = 0.86, Duration = 0.83) movements. Individual and group differences were not significant for both left- and right-hand movements, supporting group

intersession agreement.

Conclusion

This study demonstrates a setup with robust EEG and kinematic features across sessions in healthy individuals, providing some assurance of its reliability for use in longitudinal assessments. We aim to test this on a larger cohort.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.03/D14

Topic: E.04. Voluntary Movements

Support: NIH U01-NS128612

Title: Functional connectivity of the human Rolandic Motor Association Area

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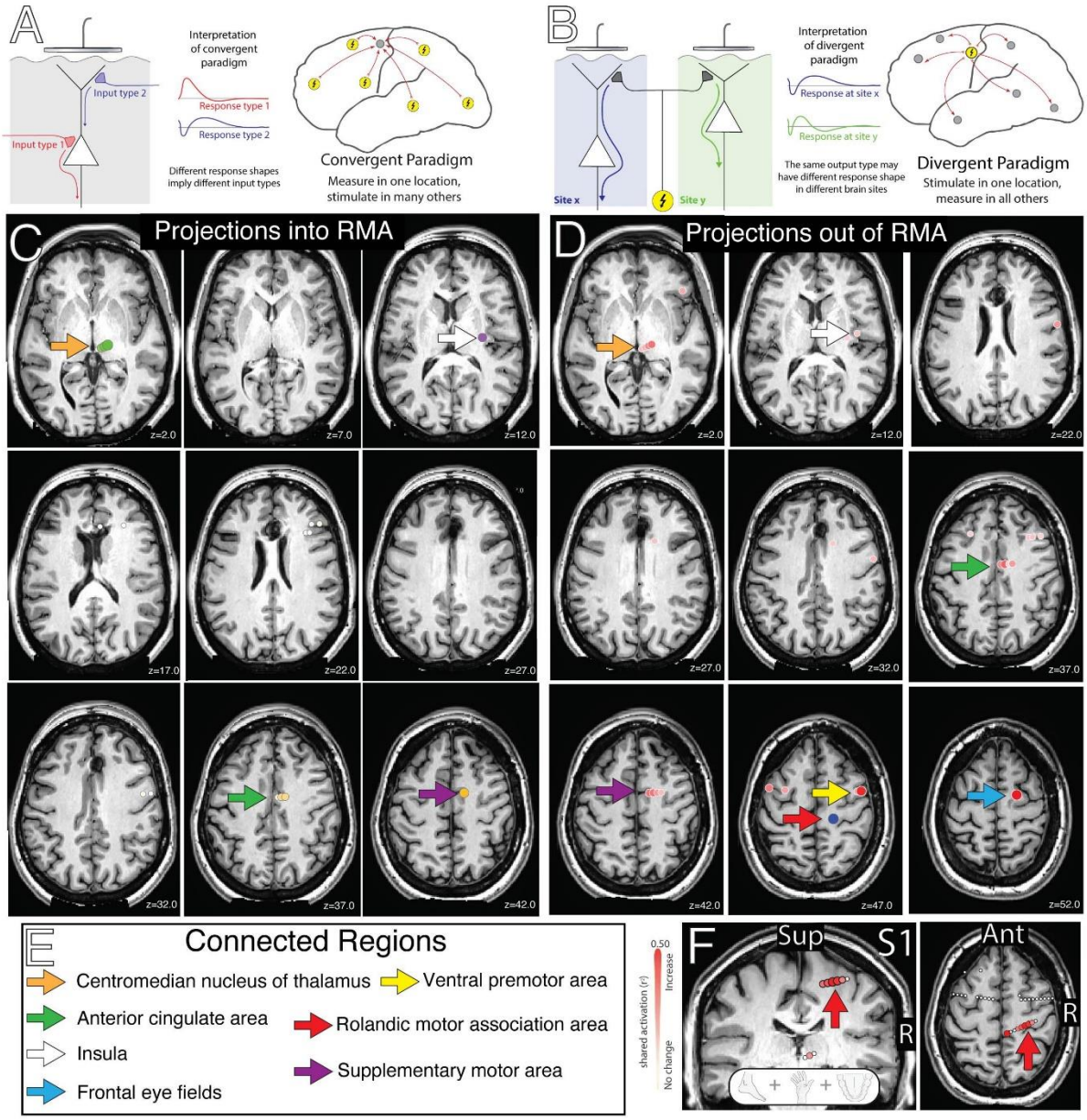
Abstract: Introduction: The Rolandic Motor Association (RMA) area is a cortical region in the depths of the central sulcus that is active prior to and during movement as recently described by our group1. The functional connectivity of the RMA is not yet understand. We applied single pulse electrical stimulation (SPES) using stereoelectroencephalography (sEEG) electrodes to identify and quantify the functional connectivity of the RMA to the rest of the brain. **Methods:** Eleven subjects (6 female) participated in a block design motor screening task in which they moved their hand, tongue, or foot in response to visual cues. For each sEEG channel we calculated the r^2 correlation of 65-115Hz power, a correlate of local neuronal activity, to EMG and identified the RMA area, defined as a region in the depths of the central sulcus with significant ($p < 0.05$), non-zero r^2 for all movements. SPES entailed a single biphasic stimulation at 6mA, 200μs pulse width repeated 12 times every 3-7 s. All evoked responses were high passed at 0.05Hz, bipolar re-referenced, and baseline corrected (500-15 *ms* prior to stimulation). In each subject, SPES was performed for channels within (n=3) and outside (n=10) the RMA. Projections into and out of the RMA were identified using the BPC[2] and CRP[3] methods respectively. **Results:** The RMA both receives and sends extensive projections from and to several distant cortical sites. The RMA shows robust connections to the centromedian and anterior nucleus of the thalamus, the insula, primary motor cortex (M1), supplementary motor area, and anterior cingulate (motor cingulate). The strength of these connections varies across

subjects, indicating differential influence from and on the RMA.**Conclusion:** The Rolandic Motor Association area is extensively connected with distant regions of the human cortex including the motor network.1. Jensen et al: https://doi.org/10.1038/s41593-023-01346-z; 2. Miller et al: DOI:10.1371/journal.pcbi.1008710; 3. Miller et al: DOI:10.1371/journal.pcbi.1011105



Disclosures: M.A. Jensen: None. **H. Huang:** None. **G. Ojeda Valencia:** None. **M. Montoya:** None. **N. Bryson:** None. **P. Brunner:** None. **J.T. Willie:** None. **D. Hermes:** None. **K.J. Miller:** None.

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.04/D15

Topic: E.04. Voluntary Movements

Support: NHMRC Grant 1194937
ARC Grant IC190100020

Title: Cortical contribution to coordination of shoulder muscles: Organisation by muscle or function?

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Abstract: Coordinated shoulder movement involves coactivation of the rotator cuff muscles to control glenohumeral translation/rotation during activation of major muscles that generate torques. Involvement of the primary motor cortex (M1) in this coordination is unclear. "Functional somatotopy" of M1 has been suggested, which implies muscles are controlled by multiple brain regions that serve different functions, and multiple muscles involved in a task are controlled by a common region. We hypothesized that: 1) M1 representation of middle deltoid (MD; prime mover) and subscapularis (SS: rotator cuff) would differ when the muscles perform different tasks, 2) M1 representation of MD and SS would overlap when active in the same task, and 3) M1 representations would have little overlap when MD and SS are active in different tasks. The left-side M1 representations of MD and SS were mapped with transcranial magnetic stimulation (TMS) in 15 right-handed healthy adults. MD and SS electromyography (EMG) was recorded with intramuscular electrodes. Participants performed isometric shoulder abduction (ABD) for MD, and internal rotation (IR) for SS in 90° abduction at 2% of maximal voluntary contraction. Hotspot and active motor threshold (aMT) were identified for each muscle. Rapid TMS mapping generated maps for MD or SS during ABD or IR. For each of the 4 maps, ~100 stimuli were delivered over a 6x7cm grid at 120% aMT of the target muscle. After map interpolation, we calculated area of map with intensity above 10% the peak amplitude for each map and the area of overlap between the maps (percentage of summed total area) for the same muscle in different tasks, different muscles in the same task, and different muscles in different tasks. We also identified the combination of M1 maps with greatest summed intensity in the overlapped area. Results show that overlap area of M1 representations was small for all comparisons and not different between comparisons ($P>0.05$; single muscle in different tasks - 7.4(3.5)% overlap as a proportion of summed maps; different muscles in single task 10.7(6.8)% overlap; different muscles in different tasks - 7.3(3.2)% overlap). The greatest intensity within overlapped areas differed between comparisons (single muscle in different tasks - 9/15 participants; different muscles in a single task - 3/15; different muscles in different tasks - 3/15). These data show that the area of overlap of M1 maps generated using TMS were small, regardless of the combination of muscles or tasks. Comparison of the intensity of the area of overlap suggests organisation related to "muscle" rather than "function".

Disclosures: P.W. Hodges: None. **Y. Ma:** None. **W. van den Hoorn:** None. **G. Nardese:** None. **G. Kerr:** None.

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Program #/Poster #: PSTR119.05/D16

Topic: E.04. Voluntary Movements

Support: DFG Grant 425899996

Title: A domain-general representation of serial order across motor and perceptual tasks in human magnetoencephalography

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Abstract: Recent research on the planning of sequential actions suggests that before movement onset, representations of upcoming sequence elements (e.g. which finger to press) exhibit a parallel organization. This can represent not only sequence-specific information but also abstract positional information (i.e. which position in the sequence). We extend this view by investigating the sensory elements associated to actions. Actions lead to sensory consequences, also termed action effects, e.g. playing a melody on a piano. It is possible to prepare an action by anticipating its effects, as in a typical case of feed-forward goal-directed action. This is explained by Ideomotor theory, which posits that after adequate exposure to response-effect mappings, actions, and their effects share a common representational space. We hypothesized that anticipated action effects are governed by the same principle of parallel organization of sequential action preparation. In this study, 23 young adult humans learned to produce from memory two 5-element sequences on a tone-producing keyboard, resulting in a coupling of actions with their auditory effects. We recorded magnetoencephalography data in a separate session with three blocked conditions: 1) motor sequence production as experienced during learning, 2) motor sequence production but muted, and 3) passive listening to the tone sequences of the associated motor sequences. In all conditions, each trial started with a visual cue indicating the upcoming sequence, followed by a preparation time window. With a multivariate pattern analysis approach, we trained a classifier to discriminate individual elements of the sequence (either individual finger presses during sequence production, or individual tones during passive listening) and tested for a parallel representation of those elements during the preparation time window. First results of this ongoing study reveal a parallel organization during preparation in all conditions, consistent with our hypothesis that action effects are also organized in parallel,

similar to their coupled actions. However, we discovered a domain-general parallel preparation of not only action-related sequences but also of purely perceptual sequences of stimuli, since a control cohort (currently N=12 and ongoing), which underwent perceptual learning of the tone sequences through passive listening without any motor task associated, showed the same parallel preparation for tone sequences. This novel finding extends the principle of parallel preparation of sequences from the motor domain to perceptual domains, suggesting a higher-order abstract representation of sequences of events.

Disclosures: A. Karagiorgis: None. **A. Das:** None. **K. Kornysheva:** None. **E. Azañón:** None. **M. Stenner:** None.

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

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Program #/Poster #: PSTR119.06/D17

Topic: E.04. Voluntary Movements

Title: Localizing joint-specific motor activity in the primary motor cortex of ambulatory individuals with a wireless cranial implant and limited electrode configurations

Authors: L. TAQUET[1], B. J. CONWAY[2], *T. F. BOERGER[1], K. GOETSCHEL[1], S. C. YOUNG[1], N. BOTROS[3], B. D. SCHMIT[4], **M. O. KRUCOFF**[1];
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Abstract: Task-specific increase in high gamma (70-120Hz) power of electrocorticography (ECoG) represents local neuronal activity and has been used to localize functional cortex, such as primary motor (M1) and speech areas. As such, high gamma localization may be a useful technique to track cortical plasticity in ambulatory individuals over time, which has become of recent interest for individuals receiving chronic neuromodulation. However, the ability to localize specific functions given the limitations of current FDA-approved cranial implants, such as the Responsive Neurostimulation® System (NeuroPace, Inc.) with only 8 available electrodes, 4 recording channels, and a fixed 250 Hz sampling rate and proprietary filter, is unproven. Here we demonstrate our ability to localize the source of movement-specific high gamma power along the well-known somatotopy of M1 in ambulatory individuals with RNS implants using a common and novel recording montage. Three individuals with implanted RNS devices with electrodes over M1 performed 40 to 50 repeated, isolated movements of the wrist, elbow, shoulder, hip, and knee while ECoG was streamed from their devices. Each four-electrode lead was recorded from independently with the ferrule as the common reference (monopolar), as well as with the more commonly used paired electrode (bipolar) reference setting. ECoG was aligned to movement onset using electromyography (EMG) and joint inertial monitoring unit data (IMU). The data from each channel in 4-second peri-movement windows was wavelet transformed, aligned to movement onset, and averaged across trials. The high gamma power time

series was then extracted and converted into EEGLAB *.set file format for importing into BrainStorm. The MATLAB toolbox BrainStorm was used to compute sources for the high gamma signal across each joint type. The source computation method used was loose constraint dynamical Statistical Parametric Mapping (dSPM). Patient cortical surface and electrode locations were extracted from deidentified CT and MRI scans. We were able to localize the source of high gamma to the precentral gyrus along the expected medial-to-lateral somatotopy of knee, hip, shoulder, elbow, and wrist along the precentral gyrus for all three participants when using the novel monopolar recording montage. Here we demonstrate the first cortical localization of joint-specific areas of M1 recorded in ambulatory individuals with limited available electrode configurations using a novel recording montage and localization technique, suggesting it may be feasible to track relative neuroplasticity over time using this method.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: NIH NINDS 1F31NS131020
NIH NICHD R01 HD095975

Title: Age-related differences in M1 intracortical inhibition and facilitation

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Abstract: Previous studies show that there are age-related differences in long- (LICI) and short-interval cortical inhibition (SICI) and intra-cortical facilitation (ICF) in resting hand muscles, however there is limited data in lower extremity muscles, as well as limited information regarding test-retest reliability of paired pulse transcranial magnetic stimulation (TMS) measures. The purpose of this study was to evaluate the effects of aging on SICI, LICI, and ICF in bilateral resting hand muscles and ankle muscles, and across 2 test-retest sessions. Data were collected on 15 Young adults (YA, 18-30 years) and 15 older adults (OA, 65-90 years) with no neurologic diagnosis. We used paired pulse TMS to calculate SICI, LICI, and ICF (ratio of conditioned versus unconditioned motor evoked potential (MEP) amplitude) in bilateral first dorsal interosseous (FDI) and left tibialis anterior (TA) and Soleus (Sol) muscles. We also evaluated suprathreshold MEP amplitudes for each muscle as a measure of corticospinal output. The paired pulse inter-stimulus intervals were 2 ms, 100ms, 12 ms, respectively for SICI, LICI,

and ICF. To date, our analysis of suprathreshold mean MEP amplitudes in YA (0.89±0.69) vs OA (1.75 ± 1.51) do not show significant differences (p= 0.11). Ongoing analysis of paired-pulse parameters is testing the hypothesis that SICI, LICI and ICF will show differences with aging, as well as between upper versus lower limb muscles. To better understand the effects of aging on volitional force generating ability of hand and leg muscles, it is important to elucidate changes in intra-cortical circuits that influence M1 output. The long-term goal of this research is to address knowledge gaps in our understanding of how healthy aging affects cortical and sub-cortical motor circuit interactions to enhance and develop neurobiology-informed rehabilitation and neuromodulation interventions.

Disclosures: M. Muthukumar: None. **O.O. Aloba:** None. **J. Spencer:** None. **J. Hope:** None. **T. Kesar:** None.

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant

Title: Effects of cannabidiol on human motor cortex circuitry

Authors: A. RAJAEI, C. A. ELLINGSON, J. WHITE, J. SINGH, J. NEARY, *C. S. MANG; Fac. of Kinesiology and Hlth. Studies, Univ. of Regina, Regina, SK, Canada

Abstract: There is growing interest in the effects of cannabinoids on the nervous system and their potential application for pain management in athletes. Studies using transcranial magnetic stimulation (TMS) indicate that cannabis use and chronic neuropathic pain are each linked to changes in excitatory and inhibitory neural circuits in the human motor cortex. Yet, no prior research has specifically considered the effects of cannabidiol (CBD), a key compound in the cannabis plant, on excitability of the human brain. The purpose of this work is to determine whether oral administration of CBD influences the balance between excitation and inhibition in the human motor cortex. The research is being conducted ancillary to a larger dose-escalation placebo-washout study of CBD administration in young, healthy male contact sport athletes (planned n =40). TMS is applied at baseline, after two weeks of placebo administration, and after two weeks of each of the planned CBD doses (5-30 mg/kg of body weight in 5 mg increments). Using paired pulse TMS, we assess intracortical facilitation (12 ms inter-stimulus interval) and short-interval intracortical inhibition (2 ms inter-stimulus interval) and determine the excitation:inhibition ratio at baseline, after placebo, and after each two-week dose escalation period. Conditioning and test stimuli are delivered at 90% and 120% of resting motor threshold, respectively. To date, 34 male, contact sport athletes have enrolled in the study (mean age: 22.6±2.7 years, mean weight: 101.2±22.4 kg). TMS assessments have been completed at all time

points up to the post 5mg/kg dose on fourteen individuals, and up to the post 10 mg/kg dose time point on seven individuals. Two outliers were identified (mean±3SD) and removed from dataset. Mean excitation:inhibition ratios were 4.82±4.84, 5.88±4.64, and 13.73±22.44 across the baseline, post placebo, and post 5 mg/kg dose time points (n=11), respectively, and 3.93±2.98 (n=6) at the post 10 mg/kg dose time point. With ongoing data collection and analyses, this work will further elucidate the influence of oral CBD consumption on human motor cortex circuitry.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI Grant number JP20K23298
JSPS KAKENHI Grant number JP24KJ2126

Title: The motor map area in the contralesional hemisphere is associated with the quality of motor control of paretic upper limb in individuals with stroke

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Abstract: Transcranial magnetic stimulation (TMS) mapping has been used to noninvasively measure the cortical representation in the motor cortex. The representation area, i.e. the motor map area, is known to be associated with the motor function after stroke. However, motor function assessment using clinical tools such as Fugl-Meyer Assessment (FMA) measures performance including compensatory movements which can be a confounding factor in the relationship. The association between motor map area and the quality of motor control, an ability of coordinated multijoint movements with minimum compensation, has not been well investigated. Here, we aimed to investigate the relationship between motor map area and the quality of motor control after stroke.Twenty subacute stroke patients (68.7±17.3 years) participated in this study. Motor map area, motor control, and motor function were evaluated at admission to and discharge from the rehabilitation ward. For TMS mapping, electromyography was recorded from five muscles in each upper limb at rest, and motor map area of each muscle was calculated offline. To evaluate motor control, visually-guided reaching task was conducted with the affected arm using a robotic device capable of horizontal motion with full gravitational support. Movement time, path length ratio (index of smoothness), and maximum speed were used as parameters for the quality of motor control. Motor function was assessed using the FMA.

Spearman's rank correlation coefficient was used to test the associations between the motor map area and each movement parameter of the reaching task as well as FMA score at admission and change from admission to discharge. At admission, the participants who had a larger motor map area within the contralesional hemisphere showed shorter movement time during the reaching task (flexor carpi radialis: ρ=-.63; abductor digiti minimi: ρ=-.57). Moreover, an increase in the motor map area within the contralesional hemisphere was associated with an improvement in the smoothness of the reaching movement (flexor carpi radialis: ρ=-.62).
The cortical excitability within the contralesional hemisphere might contribute to the coordinated movements of the affected arm. Furthermore, cortical reorganization in the contralesional hemisphere may play a key role in improving motor control after stroke.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

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Program #/Poster #: PSTR119.10/D21

Topic: E.04. Voluntary Movements

Title: Tracking multiple parameters of the corticospinal excitability profile (CEP) in humans using monophasic transcranial magnetic stimulation (TMS) at acquisition speeds of up to 2Hz

Authors: *M. KOLTZENBURG[1,2], L. CAGI[3], G. SAMUSYTE[4], J. HOWELLS[5], B. CENGIZ[6], H. TANKISI[7], H. BOSTOCK[8];
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Abstract: Paired pulse transcranial magnetic stimulation (TMS) paradigms are increasingly used as diagnostic tools and neurophysiological biomarkers in a variety of neurological diseases. Most equipment delivering single- or paired-pulse *monophasic* stimuli, including the widely used BiStim^2 (Magstim Company Ltd) is limited to inter-train intervals (ITI) of longer than 4s. Here, we investigated the feasibility to deliver stimulation at almost 10 times that speed. We used a DuoMAG MP-EEG Dual (Dyemed Diagnostic) connected to a liquid cooled figure-of-eight coil (70BF-LQC) and a D440 amplifier (Digitimer Ltd) which were controlled by QTMS software (QTMS Science Ltd). Using threshold tracking or amplitude averaging, we studied standard single and paired pulse protocols. A novel multitracking paradigm allowed the study of multiple excitability parameters over time at stimulation frequencies of up to 2 Hz. When tested on the bench, single monopolar stimuli at 2 Hz could be delivered up to 70% maximal stimulator output

(MSO) for over 1000 stimuli. Paired pulse outputs at interstimulus intervals (ISI) of 2.5 ms and 63/90 and 42/60 %MSO could be delivered at ITIs of 1.5 s or 0.75 ms, respectively, for over 1000 stimuli. The different stimulus frequencies had negligible effect on magnetic output as assessed with a search coil. Motor evoked potentials were recorded from the right first dorsal interosseus muscle of healthy volunteers and magnetic stimulation was applied in PA direction with the coil angled at 45°in the parasagittal plane. Multitracking of the motor thresholds showed substantial fluctuations at rest and substantial reductions of 5-10% MSO and rebound after voluntary contractions. Thresholds of 50, 200 and 1000 µV did not always fluctuate in parallel. We measured conventional amplitude short-interval intracortical inhibition (SICI) and parallel threshold tracking at interstimulus intervals (ISI) of 1-3.5ms delivered in ten balanced shuffled sequences. Conditioning stimuli were 70% RMT200. In A-SICI, the test stimulus was 1000µV, in T-SICI the target was 200µV using ITIs of 4.5, 3 and 1.5 s. SICI curves overlapped for all three ITIs and there were no statistically significant differences for any of the ISIs. Subjects tolerated faster stimulation rates generally well and some individuals expressed a preference for them. We conclude, that the combined use of QTMS software and DuoMAG hardware allows the acquisition of complex TMS protocols at an unprecedented speed. There are no qualitative or quantitative statistical differences in the results of A-SICI or T-SICIp protocols used in routine clinical practice at ITIs as fast as 1.5s.

Disclosures: M. Koltzenburg: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Director of QTMS Ltd. **L. Cagi:** None. **G. Samusyte:** None. **J. Howells:** None. **B. Cengiz:** None. **H. Tankisi:** None. **H. Bostock:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Director of QTMS Ltd.; Royalties for Qtrac.

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: NIH Grant NINDS R01 NS123115

Title: Reaction times in the dominant hand correlate with ipsilateral primary motor cortex GABA concentrations

Authors: *H. NISHIO, C. G. WADSLEY, C. HORTON, I. GREENHOUSE;
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Abstract: The influence of gamma-aminobutyric acid (GABA) within the primary motor cortex (M1) on reaction time is uncertain. Given GABA’s role as a primary inhibitory neurotransmitter, a potential function within M1 is to resolve competition amongst motor representations for

efficient movement execution. Competition resolution may be important when motor representations are neighboring one another within M1 and less so for competitions between contralateral homologous M1 representations. This study explored the hypothesis that M1 GABA is important for resolving competition when choosing between responses within the right hand but not between the hands, with the prediction individuals with higher M1 GABA concentrations would have faster within-hand choice reaction times. We recruited 31 healthy adult human participants to complete instructed-delay two-choice reaction time tasks involving response choices either within the right hand (index vs pinky) or between the hands (left index vs right index) while measuring behavioral button press reaction times. We then used edited magnetic resonance spectroscopy (MRS) to measure GABA concentrations in left and right M1 as well as a control occipital lobe voxel. We then calculated Pearson's r correlations between reaction times for each type of response and GABA concentrations in our three regions of interest.Preliminary analyses showed no correlation between left M1 GABA and reaction times, regardless of response type (all BF10 < 0.43). However, higher right M1 GABA estimates correlated with faster reaction times when choosing between responses within the ipsilateral right hand (r = -0.320, BF10= 1.866) as well as for right hand (r = -0.386, BF10= 3.937) but not left hand responses (r = -0.264, BF10= 1.095) when choosing between hands. There were no correlations between GABA in occipital lobe and all response types (all BF10 < 1.0). Our findings suggest right M1 GABA, ipsilateral to the responding hand, facilitates the execution of prepared responses, independent of whether response choices are within one hand or between the two hands. Given our participants were right-handed, this may reflect a GABAergic mechanism associated with functions of the non-dominant M1. Thus, intrinsic M1 GABA concentration ipsilateral to the dominant hand may serve a special role in mediating the execution of a prepared response.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: NIH Grant DA048742
NIH Grant NS126044
NIH Grant NS111028

Title: Spatio-temporal mapping of motor behavior on the mouse cerebral cortex

Authors: *L. POPA[1], R. CARTER[2], E. FLAHERTY[3], A. K. NIETZ[2], T. J. EBNER[2];
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Abstract: As brain function arises from global integration of local processes, monitoring the activity across a large area of the cerebral cortex during self-directed complex motor behavior provides insights into how the brain processes information. Chronic implants of optically clear, polymer skulls allow access to large areas of the dorsal cerebral cortex (~49 mm^2) in Thy1-GCaMP6f mice, expressing GCaMP6f in excitatory neurons. Dual wavelength, long-term mesoscopic cerebral cortical activity (20 Hz in 5 min trials) was performed in head-fixed, water restricted mice (n=5) trained to reach for a waterspout on cue. High-definition video cameras recorded behavior and eye pupil at 80 Hz that were quantified off-line using machine learning algorithms. The hemo-corrected cerebral Ca^{2+} activity was functionally segmented into Independent Components (ICs) and the IC time-courses were used to construct Generalized Linear Models (GLMs) examining for behavior encoding and decoding. We extracted behavioral measures including paw and nose tip position along x and y directions (PX, PY, NX, NY, respectively), eye pupil area (A), and distance from paw to mouth (P2M). Behavior encoding and decoding at lead/lags (±10 sec) was assessed between neural activity and behavior. Decoding model quality was assessed by the cross-correlation between the reconstructed and the real parameter. Reach evoked wide-spread cortical modulation, with single IC peak R^2 ranging from 0.03 to 0.5 (0.21 ± 0.11). The cortical sensitivity maps show each parameter being encoded in a multitude of functional areas including premotor, motor, somatosensory, visual, and retrosplenial. Encoding starts ahead of behavior at -10 s for A, -6s for P2M, -2 s for PX, -1 s for the rest of parameters and persists to 0 s for A, 2 s for PX, PY and NY, 4 s for NX, and 6 s for P2M after behavior. There was robust decoding, with the Pearson's correlation reaching 0.8 for PX and P2M, 0.5 for NY, and A. For PY and NX, decoding performance was below 0.3. Decoding model maps show a dynamic evolution of the cortical areas involved for each parameter. Decoding time courses are specific for each parameter, ranging from -5 to 4 sec. relative to behavior, all show that paradoxically, decoding based on preceding brain activity lags the behavior, while decoding based on lagging activity precedes the behavior, suggesting the cortex anticipates the sensory consequences of future behavior and stores a memory of the planned behavior. The results show different behavioral measures have specific spatio-temporal cortical representations and provide insights into the mechanisms of motor planning, execution, and memory.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.13/D24

Topic: E.04. Voluntary Movements

Support: NIH NINDS R01NS131227 (PI: Vahdat)
Florida Department of Health James and Esther King Biomedical

Research, Award Number 23K07 (PI: Vahdat)
NIH award, S10 OD021726

Title: Brain wide activation and connectivity analysis in awake mouse fMRI during forepaw force control

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Abstract: Introduction: Controlling the level of upper limb force is crucial for performing daily activities. Despite knowing the areas involved in motor skill learning the neural mechanisms involved in learning appropriate force control are not well understood.Functional magnetic resonance imaging (fMRI) in rodents allows unbiased tracking of whole-brain activation maps during learning to pinpoint key cortical, subcortical, and brainstem structures. However, there are no published fMRI studies performed during a motor task in mice. To fill this gap, we developed a novel MR-compatible head fixation apparatus for awake mouse fMRI during the forepaw force control task, enabling us to shape mice during motor behavior while minimizing noise and motion artifacts.Methods: We built an accurate (resolution 0.005 N) MR-compatible miniature force transducer and a 3D-printed head fixation system to shape and allow mice to engage in the forelimb force control task. We also designed and built a saddle linear MRI coil to fit our head fixation system. The training paradigm involves wild-type water-deprived mice undergoing a reward-based forepaw press/no-press the force transducer task for 7-14 days. After the training days, mice underwent an event-related awake SE-EPI fMRI scan while performing the right forepaw press task.Results Aggregated fMRI activation maps across 15 animals revealed significant ($p<0.05$, corrected) brain-wide activation related to forelimb force control across different cortical, subcortical, and cerebellar regions. The cortical structures mainly included M1, M2, ACC, RSG, and S1. The visible activation in subcortical structures included STR, hypothalamus, THL-VPL, THL-VL, SC & and IC. In the cerebellum, significant activation clusters were observed in Crus1 and the SIM lobules. Partial correlation analysis was used on average activation within each distinct region, accounting for task paradigm effects, to assess the functional connectivity. The connectivity revealed significant correlations among various cortical and subcortical sensorimotor areas, including the thalamus and striatum. Positive correlations were noted between cortical and brainstem structures.Conclusion: Overall, our proposed method shows the feasibility of awake mouse fMRI in forelimb motor control and provides evidence for a widespread network of cortical and subcortical areas activated during force control. The functional connectivity analysis further helps us in determining functional interaction across various brain regions. This method can further be used to study brain network reorganization following movement disorders and stroke in mice.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Program #/Poster #: PSTR119.14/D25

Topic: E.04. Voluntary Movements

Support: Deutsche Forschungsgemeinschaft (DFG)

Title: Aging-related connectivity changes in the motor system

Authors: *F. WULLENKORD[1,2], M. BARDAKAN[1], V. WUNDERLE[2], T. D. KUZU[2], C. GREFKES[3], P. H. WEISS[1,2], G. R. FINK[1,2];
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Abstract: Several motor functions decline with aging. This study examines neural activity and connectivity changes in the primary motor cortex (M1), using fMRI data from 125 healthy participants (age: 56.5 ± 17.4 years, range: 18-90 years) performing unimanual finger tapping movements at maximum speed. We analyzed the BOLD response and interhemispheric connectivity through task-related functional connectivity (FC) and generalized psycho-physiological interactions (gPPI). Further, we explored with Dynamic Causal Modelling (DCM) whether connectivity changes in the motor system modulated the aging-related decline in motor functions. Aging was associated with decreased M1 lateralization and increased ipsilateral M1 activity during finger tapping. Older participants showed higher M1-M1 connectivity, with a more significant modulation of contralateral M1 by the ipsilateral M1 when using the dominant hand. The results of the DCM analysis suggest that enhanced connectivity mitigates the aging-related decline in tapping speed. Our findings suggest that aging-related reduced lateralization and increased interhemispheric connectivity in the motor system potentially reflect compensatory adaptations in the motor network associated with aging.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

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Program #/Poster #: PSTR119.15/D26

Topic: E.04. Voluntary Movements

JST, PRESTO Grant Number JPMJPR23I1
JST Moonshot R&D(JPMJMS2012)

Title: Neurofeedback of sensorimotor rhythm magnitude for shortening motor reaction time: A Double- Blind Sham-Controlled Study

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Abstract: Quickly responding to stimuli and generating motor output are foundation of the specialized skill for competitive sports and e-sports. To train this, neurofeedback training (NFT) has been proposed. NFT enables individuals to voluntarily induce excitable state in the primary motor cortex (M1), by providing event-related desynchronization (ERD) of electroencephalogram (EEG) derived from M1, namely sensorimotor rhythm (SMR). Since the SMR-ERD is an index of corticospinal tract excitability related to motor generation, NFT is believed to be effective in shortening simple reaction time (RT). However, the necessity of feedback based on one's own EEG changes remains unclear. Here, we examined the change in neural excitability of the motor-generating pathway by comparing the reaction time of voluntary muscle output before and after NFT in a double-blind sham-controlled study design.Twenty-two right-handed healthy adults were assigned to the experimental and control groups (11 subjects each), and changes in the mean RT based on electromyography (RT-EMG), pressure sensor (RT-Pressure), and button (RT-Button) were examined before and after NFT. Using a portable EEG, we calculated the SMR-ERD magnitude of the EEG derived from M1 in the left hemisphere (C3), and developed sonification-based neurofeedback in which the stronger the ERD was associated with the higher feedback tone. We evaluated RT before and after NFT. The experimental group received auditory feedback based on their EEG in real time during NFT, while the control group received feedback based on EEG of others recorded beforehand.To examine the efficacy of NFT, we performed time-frequency analysis for EEG signals during the NFT. We confirmed that training resulted significant difference in the number trials that participants induced ERD between the experimental and control groups ($p < 0.05$; repeated measures two-way ANOVA). Moreover, group-level behavioral performance was significantly different in both the RT-Pressure and RT-Button (Figure 1, $p < 0.05$; repeated-measures two-way ANOVA). This indicates that NFT using one's own EEG is effective in training the self-induction of ERD, while the placebo presented to the control group delayed RT due to factors such as mislearning by preventing the induction of appropriate motor-related brain activity.

Disclosures: H. Tanaka: A. Employment/Salary (full or part-time):; LIFESCAPES Inc. **J. Ushiba:** A. Employment/Salary (full or part-time):; LIFESCAPES Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LIFESCAPES Inc. **S. Iwama:** A. Employment/Salary (full or part-time):; LIFESCAPES Inc..

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.16/D27

Topic: E.04. Voluntary Movements

Support: DFG Grant 431549029 – SFB 1451

Title: Dynamic connectivity changes relate to apraxia in Alzheimer's disease

Authors: *T. D. KUZU[1], E. JAEGER[2], A. K. BONKHOFF[3], V. WUNDERLE[1], G. N. BISCHOF[4,5], K. GIEHL[4,5], M. H. T. SCHMIESCHEK[1], O. ONUR[1], G. R. FINK[1,6], A. DRZEZGA[4], P. H. WEISS[1,6];
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Abstract: Apraxia affects cognitive motor functions related to gesture imitation, pantomiming as well as actual object use and is commonly observed in individuals with Alzheimer's disease (AD). Previous investigations suggest that apraxia results from lesions in praxis networks located in the motor dominant hemisphere. However, the underlying mechanisms are not fully understood. This exploratory study investigated how changes in the brain's functional connections relate to apraxia in individuals with AD. We hypothesized that apraxic impairments in individuals with AD are associated with altered connectivity patterns in the praxis networks. We collected resting-state functional MRI data from 13 individuals with AD pathology, as confirmed by positive amyloid and tau markers, who underwent extensive cognitive, motor, and apraxia assessments. We also included 13 healthy participants for comparison. Using independent component analysis (ICA), we analyzed the static and dynamic functional connectivity (FC) patterns of resting-state networks and examined how they correlate with apraxia scores. Our analysis revealed two dynamic FC states across our study population, namely a state characterized by weaker connectivity and more integration, as well as a state characterized by stronger connectivity and more segregation. After correction for multiple comparisons, there were no significant group differences regarding correlations in static and dynamic FC. However, individuals with AD tended to spend more time in the state with more integration in consecutive time windows without switching to the other state and spent a higher proportion of time in this state across the entire scan duration. These temporal dynamic connectivity measures correlated significantly with deficits in apraxic imitation deficits. Our results suggest that apraxic imitation deficits in AD are associated with altered dynamic rather than static functional connectivity of resting-state networks.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: CIHR Grant MOP-68812
CFREF Grant 2022-00010

Title: Parallel coding of intrinsic and extrinsic movement plans in parietofrontal cortex: an MEG study

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Abstract: It is sometimes assumed that that the brain must first convert sensory inputs into extrinsic movement plans before computing intrinsic muscle commands tuned for current limb posture. Where, how and when this happens in the human cortical arm movement planning network remains largely unknown. Here, we use high spatiotemporal resolution magnetoencephalography (MEG) combined with a pro-/anti-wrist pointing task with 2 opposing forearm postures to investigate this question. First, we computed cortical source activity in 16 previously identified bilateral cortical areas (Alikhanian, et al., Frontiers in Neuroscience 2013). In previous studies we compared pro/anti trials to identify a posterior-anterior sensorimotor progression from α / β band sensory activity to β-band motor activity, followed by a 'recurrent' anterior-posterior progression of the motor code (Blohm, et al., Cerebral Cortex 2019), and showed how these signals are integrated into hand-specific activity (Blohm, et al., J Neurophysiol 2022). Here, we contrasted oscillatory activity related to opposing wrist postures to find posture coding and test when and where extrinsic and intrinsic motor codes occurred. We found a distinct pair of overlapping networks coding for posture (in γ band) vs. posture-specific movement plans (α and β). Some areas (e.g., pIPS) only showed extrinsic motor coding, others (e.g., AG) only showed intrinsic coding, but the majority showed both types of codes in parallel. In those that coded both, intrinsic coding generally appeared first, and intrinsic coding appeared first overall in area POJ (around 180ms after target cue presentation). These findings are consistent with a direct feed-forward transformation from sensory to intrinsic motor coordinates for rapid control combined with parallel computations of extrinsic motor coordinates for use in higher-level aspects of visually-guided action, such as spatial updating and internal performance monitoring.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: Canadian Institutes of Health Research (CIHR)
Vision: Science to Applications (VISTA) program

Title: Cortical Modularity and Integration of Multimodal Cues for Reach: an fMRI / Graph Theory Approach

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Abstract: Real-world behavior requires the integration of multiple cues for coordinated action, for example object location cues to aim a reach combined with object-orientation cues to form a correct grasp. To understand how the brain might integrate these different sensory and motor components, we employed a cue-separation event-related fMRI task in which twelve participants were visually cued to the Location (L: left or right to center) of a cube, and verbally instructed how to manually Orient (O: horizontal or vertical grip), with each cue followed by a delay in randomized temporal order (OL vs. LO). We then employed standard univariate analysis and graph theory analysis (GTA) of 200 cortical nodes to understand how the cortex integrates these action cues over time. Data were analyzed separately based on three predictors: Delay 1 (between the two cues), Delay 2 (between the 2nd cue and go signal), and an Action Phase. As expected, the univariate analysis revealed that sensory-specific activation occurred during the first delay: Early Visual Cortex for the visual location instruction and Superior Temporal Gyrus for the auditory orientation instruction, followed by similar patterns during Delay 2, and widespread sensorimotor activation during the grasp period, independent of cue order. GTA revealed three network modules (spanning occipital-parietal, somatomotor, prefrontal/inferior parietal cortex), showing subtle OL/LO order-dependencies. The somatomotor module became more prominent after the second cue, finally merging with the occipital-parietal module during Action, suggesting widespread signal sharing & integration across multiple sensorimotor areas. When the overall upward trend in BOLD progression was excluded from the data, the three modules remained highly segregated and stable for all three predictors, suggesting that the trend reflected the sensorimotor integration process. In conclusion, these data suggest that several cortical modules are involved in processing multimodal cues for action, whereas the overall trend in cortical activation signifies cue integration for coordinated action.

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Poster

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Support: NIH Grant P30 DA048742
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NIH Grant R01 NS111028

Title: Cortex-wide characterization of decision-making behavior during a spatial navigation task

Authors: *S. HALEY[1], D. A. SURINACH[2], S. B. KODANDARAMAIAH[3], T. J. EBNER[4]; [1]Univ. of Minnesota, Minneapolis, MN; [2]Mechanical Engin., Univ. of Minnesota Twin Cities, Roseville, MN; [3]MECHANICAL Engin., Univ. Of Minnesota, Twin Cities, Minneapolis, MN; [4]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Decision-making behavior involves complex interactions among many cerebral cortical regions. The retrosplenial cortex, posterior parietal cortex, and secondary motor cortex have all been shown to play crucial roles in decision-making assays in rodents. However, the temporal coordination across these regions to generate a decision is less understood. We used a miniaturized head-mounted widefield fluorescence microscope (mini-mScope), to record cortex-wide Ca^{2+} dynamics of freely moving mice (n=6) during two variants of an 8-maze task. In this task, mice expressing GCaMP7f navigated the maze in an alternating pattern to receive a sucrose reward. Later, a rule change was implemented to only provide a reward on the left side of the maze. The Ca^{2+} data recorded during these paradigms was reduced into a discrete number of cortical activation states using a k-means clustering algorithm. The resulting 11 cortical states described a diverse set of activations spanning the entire dorsal cortex. Time course analysis of these state activations unveiled interesting differences in cortical dynamics between the two paradigms. A significant increase in the usage of a visual/retrosplenial cortex state occurred during the decision phase of the alternating variant compared to the left-only paradigm, suggesting a prolonged period of evidence accumulation when the reward location changes each lap. A cortical state consisting of secondary motor/posterior parietal cortex activation had a significantly higher probability during the left-only paradigm, indicating a higher confidence in the behavior-reward contingency. Distinct sequences of cortical state activations revealed that the left-only task elicited a higher probability of anterior to posterior feedback and used the posterior parietal cortex for feedforward sensory integration to a lesser extent than the alternating task. There were also patterns of cortical state motifs that correlate with mouse location in the maze. Motifs beginning in posterior cortical regions which describe an anterior flow of activity were often initiated as the mouse enters the exits the central corridor, likely signifying the start of sensorimotor transformation when the visual environment changes. Patterns of motifs characterized by a posterior flow of activation ending in sensory and visual regions were more evident at the reward spout during the left-only task, further supporting a greater utilization of feedback input during this paradigm. These findings show that mice use distinct decision-making strategies with unique spatiotemporal neural dynamics to solve two variants of the 8-maze task.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.20/D31

Topic: H.10. Human Learning and Cognition

Title: Functional Connectivity Changes Resulting from Motor Mapping Inconsistencies in Categorization

Authors: *J. MARTIS[1], S. SHARMA[2], K. JENTINK[1], H. MECHTENBERG[3], C. A. SEGER[4]; [1]Psychology, Colorado State Univ., Fort Collins, CO; [2]Psychology, Colorado Sate Univ., Fort Collins, CO; [3]Psychology, Univ. of Connecticut, Storrs, CT; [4]Psychology, Colorado State Univ. Mol., Cell. & Integrative Neurosciences, Fort Collins, CO

Abstract: The Competition between Verbal and Implicit Systems (COVIS) theory of categorization emphasizes the integration of motor responses to the onset of external events. For example, a person may associate a motor movement (touching a laptop's trackpad) in response to an event onset (screen turning dark). A limitation of the COVIS model is its specificity to static environments where event-motor mappings are consistent. It is important to test the model's generalizability within dynamic environments where the event-motor mappings are inconsistent to determine variations in neural recruitment. The current study aimed to explore brain regions involved in inconsistent mappings when the visuospatial location of response options and associated motor effectors switched randomly during categorization. The use of inconsistent mappings extends beyond COVIS' scope, allowing for the understanding of neural networks more likely to generalize in dynamic real-world environments. Univariate analysis showed significantly greater activation in the intraparietal sulcus (IPS) for inconsistent than consistent motor mapping trials. The current work used psychophysiological interaction analysis (PPI), with the IPS as a seed region, to identify distinctions in functional connectivity between consistent and inconsistent mappings. PPI analysis found greater connectivity between the IPS, the anterior cingulate cortex (ACC), and the motor hand region during inconsistent trials. PPI results contribute to the understanding of brain regions recruited to maintain neural network integrity associated with categorization processes. Categories may be learned more flexibly than simple event-motor mappings proposed by the COVIS model.

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Poster

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Topic: E.04. Voluntary Movements

Support: Honda R&D Co., Ltd.
NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc.
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Title: The ventral midbrain activity causally enhances motor output: an fMRI neurofeedback study

Authors: S. K. SUGAWARA[1], ***A. SHIINA**[2], Y. UEDA[2], Y. HOSHI[2], N. USUDA[1], J. OKUMA[2], M. NISHIJIMA[2], M. MOMOKI[4], T. IBARAKI[4], M. HOSHINO[3], Y. NISHIMURA[1]; [1]Neural Prosthetics Project, Tokyo Metropolitan Inst. of Med. Sci., Setagaya, Japan; [2]Honda R&D Co., Ltd., Wako-shi, Japan; [3]Honda R&D Co., Ltd., Wako, Japan; [4]NTT DATA Inst. of Mgmt. Consulting, Inc., Chiyoda, Japan

Abstract: The ventral midbrain (VM), which contains dopaminergic neurons, is well known to be involved in reward processing and motivation. In parallel, our recent study demonstrated that the VM premovement activity links to the strength of subsequent force generation. However, the causal role of the VM on motor performance remains unclear in humans. The aim of this study was to investigate whether the VM activity was causally involved in controlling subsequent motor output using fMRI neurofeedback. Sixty-one healthy volunteers participated in the present study. They performed a ready-set-go task with fMRI neurofeedback in a 3T-MRI scanner. This task consisted of three periods: induction, ready-set, and go. We set two conditions for the induction period: up-regulation or maintenance of VM activity. Participants were asked to voluntarily control the VM activity corresponding to the conditions with the visual feedback of their real-time activity measured by fMRI during the induction period. Following the induction period for 20 seconds, they prepared to squeeze the force grip sensor with their right hand during the ready-set period. Then, they squeezed the force grip sensor as fast as possible at the go period. This experimental design allowed us to elucidate the causal role of VM activity on subsequent motor performance. The VM activity during the induction period was significantly higher in the up-regulation condition than in the maintenance condition, confirming the successful voluntary control of the VM activity with fMRI neurofeedback. Both reaction time and peak grip force at the go period were significantly improved after the up-regulation condition rather than after the maintenance condition. On the other hand, the VM activity in the up-regulation condition varied across trials. To further investigate the causal relationship between the VM activity and subsequent motor performance, we examined the relationship between the induced VM activity and subsequent motor performance in a trial-by-trial manner using a robust regression analysis. The results showed that the amount of voluntarily-regulated VM activity was more strongly associated with peak grip strength than with reaction time. These results provide compelling evidence for the causal role of the VM on the strength of force generation, a significant advancement in our understanding of motor control.

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Nishijima: A. Employment/Salary (full or part-time):; Honda R&D Co.,Ltd. **M. Momoki:** A. Employment/Salary (full or part-time):; NTT DATA Institute of Management Consulting, Inc. **T. Ibaraki:** A. Employment/Salary (full or part-time):; NTT DATA Institute of Management Consulting, Inc. **M. Hoshino:** A. Employment/Salary (full or part-time):; Honda R&D Co.,Ltd. **Y. Nishimura:** F. Consulting Fees (e.g., advisory boards); NTT DATA Institute of Management Consulting, Inc..

Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Alvin and Marion Birnschein Foundation

Title: Effects of normative aging on upper extremity sensorimotor control

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Abstract: Sensorimotor control of visually guided movements has been widely studied in adults, yet the temporal relationships between age-related changes in brain activity and changes in clinical, kinematic, and sensorimotor control remains unclear. Understanding these relationships is important for identifying disease-related changes in brain activity that impact motor performance. 31 unimpaired adults completed the Nine Hole Peg Test (NHPT) and a Reach and Hold task using a passive wrist robot with simultaneous 64-channel electroencephalography (EEG) . During the Reach and Hold task participants used a wrist-controlled cursor to capture a visual target, which pseudo randomly moved horizontally on a screen every [3.5 5.5] sec, for 10 trials lasting 50 sec each. Reaction Time (RT) was defined as the time required to initiate movement following target displacement (TD). Overall performance delays (T_{prf}) were measured via trial-wise cross correlation between the cursor position and TD over time. Following typical preprocessing, EEG data was epoched [-1 2] sec about the TD (Visual Response) and RT (Motor Response) for each participant, baseline corrected, and averaged. The peak amplitude of each channel was used to measure the Visual and Motor Response of the task. Group differences (Young (N = 11), Middle (N = 10), and Old (N = 10)) were tested via one-way ANOVA. A piece-wise linear fit between NHPT, RT, and T_{prf} as a function of age was also performed to assess continuous changes in visually guided movements with age. EEG amplitude was

correlated with each measure to identify how they are related to changes in brain activity.NHPT, RT, and T_{prf} measures increased with age ($F \geq 3.88$, $p<0.05$) with significant differences between Old-Young and Old-Middle age groups. Piece-wise linear regression found significant increases in each measure at age 55 ($R^2 \geq 0.74$; $p<1x10^{-5}$). Visual and Motor Response amplitudes over the parietal lobe significantly decreased with age ($F \geq 3.35$, $p<0.05$) with significant differences between Old-Young groups. Parietal channels of the Visual Response were significantly correlated with increased NHPT, while those for the Motor Response were negatively correlated with NHPT, RT, and T_{prf} ($R^2 \leq -0.36$, $p<0.05$). These results highlight neural correlates to changes in sensorimotor control during normative aging. The slowing of movement with age is related to changes in neural processing and increased T_{prf}. Fully quantifying age-related changes in sensorimotor control using kinematic and neural variables may facilitate identification of disease related changes in brain function that directly impact upper extremity reach.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR119.23/D34

Topic: E.04. Voluntary Movements

Support: NINDS Grant R01 NS114046

Title: A mechanism of lateralized hand control for precision drawing: interhemispheric connections between primary motor cortex and the superior parietal lobule.

Authors: T. KIM[1], S. GASSASS[2], R. ZHOU[3], A. R. CARTER[4], I. G. DOBBINS[5], L. LIU[3], M. MCAVOY[2], Y. WANG[6], ***B. A. PHILIP**[2];
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Abstract: Dominant right hand (RH) performance depends on left-hemisphere specializations, but the specific neural mechanisms remain unknown. Here we used fMRI to identify how humans perform a dominant-hand task (visually guided drawing) with the non-dominant left hand (LH). To filter out the simple asymmetries of contralateral control, we organized our analysis around the hemispheres “ipsilateral to movement” vs “contralateral to movement” rather than left and right. We hypothesized that the superior parietal lobule (SPL) would be more active ipsilaterally during LH drawing than RH drawing, consistent with a left-hemisphere specialization that supports drawing with both the RH (when it is contralateral to movement) and

LH (when it is ipsilateral to movement). METHODS: Right-handed adult volunteers (n=33; 24 healthy controls, 9 with peripheral nerve injury to the RH) underwent fMRI scanning while performing a visually guided precision drawing task, alternating between hands. We performed two fMRI analyses on 12 *a priori* regions of interest (ROIs): 6 brain areas (primary motor cortex (M1), SPL, parietal area 7A, intraparietal sulcus (IPS), supplementary motor area, and dorsal premotor cortex) * 2 hemispheres (ipsilateral or contralateral to movement). First, we measured BOLD magnitude in each ROI with a general linear model based on 8 factors: drawing hand (LH or RH), group (control or patient), age, sex, and 4 performance variables. Second, we measured task-related changes in functional connectivity between the ROIs via generalized psychophysical interaction (gPPI). RESULTS: Our BOLD magnitude analysis revealed that SPL ipsilateral to movement was the only ROI where the factor "drawing hand" was significant, but with higher magnitude for RH drawing ($t = 2.55$, $p = 0.013$; other ROIs $p > 0.1$). Our analysis was adequately powered for this effect (power ≥ 0.9). We found no effects of group in any ROI ($p > 0.1$). Our gPPI analysis revealed that during LH drawing (vs. RH drawing), M1 contralateral to movement (i.e. acting M1) increased functional connectivity with M1 and IPS ipsilateral to movement, and decreased functional connectivity with SPL ipsilateral to movement. DISCUSSION: These results support an alternative hypothesis: ipsilateral SPL played a role consistent with a mechanism for RH performance. Specifically, during RH drawing, SPL ipsilateral to movement was more active and more connected to acting M1. We found no effects involving contralateral SPL, so this finding is not localized to left SPL or right SPL. Instead, RH-specific drawing performance (i.e. the dominant-hand advantage) may depend on interhemispheric connections between M1 and SPL.

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Poster

PSTR119: Cortical and Subcortical Pathways of Movement

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Topic: E.04. Voluntary Movements

Support: NIH R21NS114816A
University of Delaware Research Foundation 22A01471

Title: Age-related changes in brain microstructure: implications for motor performance

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Abstract: Microstructural changes in white matter (WM) structures as captured by diffusion tensor imaging (DTI) have been linked to decreased cognitive performance in the aging population. However, our understanding of how aging impacts the microstructural integrity of grey matter (GM) remains limited. A novel metric derived from DTI, known as free water-corrected fractional anisotropy (FAt), has emerged to address the influence of free water molecules in the extracellular space, a factor unaccounted for in traditional FA measurements. Here, we explored changes in FAt between young and older healthy adults, focusing on both WM and GM microstructure and their relation to performance on pegboard tasks. Participants included 20 young adults (YA) and 34 older adults (OA) matched at the group level on multiple variables. A voxel-wise analysis was performed to identify FAt differences between YA and OA. FAt values from these regions were then extracted and correlated with motor scores. Results demonstrated that OA had decreased FAt in WM regions, such as the prefrontal cortex and corpus callosum. However, OA also had increased FAt values in several GM regions, including the bilateral putamen, and higher values here were related to poorer performance on pegboard tasks testing fine motor skills. Previous interpretations of increased FA have suggested that glial scarring or Wallerian degeneration may underlie these changes. While this study cannot speak to those changes directly, our findings suggest that increased FAt in motor-related GM regions may be detrimental to hand function, which is known to decline with age.

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Poster

PSTR120: Target-Directed Movement Control

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Title: Global Increases in Firing Rates during Initial and Corrective Submovements within Primary Motor Cortex: Condition-Invariance, Cortical Activation, or Speed Tuning?

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Abstract: Precision reaching often requires a combination of initial and corrective submovements, which may have unique neural population profiles and patterns of activation. Furthermore, neural activity for each submovement may be more than condition dependent, i.e.

related to the reach direction and velocity, but also have global increases in firing rates across the neurons. Sources of increased neural activity potentially include: i) condition-invariant activation with any movement, ii) an active state for the cortical area, or iii) speed tuning for the movement. Two rhesus macaques performed a precision center-out-task with small targets. Neural activity from single units in primary motor cortex and associated behavioral data were recorded during both initial and corrective submovements. Peak hand speeds and the time-aligned individual firing rates were examined.
Firing rates for initial submovements had condition-invariant activity with the initiation of movement, which was independent of the reach location, but shifted by a time lag and had some scaling with reach speed. Interestingly, mean firing rates were higher at the completion of initial submovements than baseline levels, whereas mean firing rates were lower at the completion of corrective submovements than baseline levels. We also observed that peaks for firing rates of initial submovements were broader than those of corrective submovements, owing to larger variance in time when neurons were most active. The narrower firing rates of the corrective submovements oscillated more closely aligned to speed peaks.
Our results suggest that the neural population may remain in an *active* state after initial submovements in anticipation of subsequent corrective submovements. The neural population transitions from an *active* state to an *off* state once the precision reach is successfully completed. While increases in global firing rates corresponded to peaks in hand speed, the width of global firing rates for initial submovements did not correspond with the width of the hand speed profiles. The breadth likely represents the cortical dynamics and synaptic connections within the population before descending fibers carry signals to motor units. Our results highlight the importance of condition invariant neural activity and its unique characteristics related to both an *active* state in a cortical area as well as representation of speed.

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Poster

PSTR120: Target-Directed Movement Control

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Topic: E.04. Voluntary Movements

Support: SFB1528, Project B02

Title: Early visual responses along the cortical grasping pathway observed using Neuropixels

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Abstract: Area F5 in the premotor cortex of macaque monkeys is a major node in the cortical grasping circuit. It receives projections from visual areas like the Anterior Intraparietal area (AIP) and projects to the primary motor cortex (M1). Consequently, neurons in F5 show responses during the visual presentation of objects as potential grasping targets as well as during the execution of grasping movements. Here, we investigate the details of visual responses in neurons of the grasping network using a novel recording tool - the Neuropixels probe.We recorded activity of 1074 visually responsive neurons from area F5 in one macaque monkey during a delayed grasping task. The monkey observed a grasping target for 300 ms, then memorized the observed object for a variable duration (500 – 800 ms) and finally executed a grasping movement in the dark, i.e., without further visual feedback. We used two sets of six targets, one set of targets was designed to induce a variety of grasping movements, whereas the objects in the second set were all grasped in the same way despite large difference in their visual appearance.We found that a group of 332 (31%) neurons exhibited very short visual latencies (<70 ms) comparable to those found in the early visual cortex. The strong responses of these neurons were often transient and invariant of the presented object. A majority (54%) of the short-latency neurons responded to all six objects in a set. In contrast, neurons with longer latencies (70 – 300 ms) were more selective, 52% of them responded only to one or two of the six objects. We then investigated 408 visually responsive neurons from area AIP and found a similar proportion (32%) of short latency neurons in that area, suggesting that this signal was transferred along the visual and visuomotor processing streams. These result show, that fast – but not very informative – onset transients are not eliminated in the visual processing hierarchy but transferred up to the premotor areas like F5. It remains to be shown how these transients influence the activity on even later stages of the motor system and the grasping behavior.Interestingly, in neurons with long visual latencies, the visual selectivity for objects in the set that induced identical grasping movements was not substantially lower than for those in the set that induced differential grasping movements. This changed when the neuronal activity during the grasping epoch was investigated, where the variability of neuronal responses was much higher between objects that yielded different grasping movements. These results suggest that the visual responses in the premotor area F5 serve rather the identification of objects than the preparation of grasping movements.

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Poster

PSTR120: Target-Directed Movement Control

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Topic: E.04. Voluntary Movements

Support: NIH NCATS TL1 (TR002318)
NIH BRAIN Initiative U01 (UF1NS126485)
Simons Collaboration for the Global Brain Pilot award (898220)

Title: Spatially distributed sampling of motor cortex during reaching

Authors: *R. CANFIELD[1], T. OUCHI[1], L. R. SCHOLL[2], P. RAJESWARAN[3], L. I. SMITH[1], A. L. ORSBORN[4];
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Abstract: Evidence from multi-neuron-resolution mapping studies suggests that movement related information is not uniformly distributed across frontal motor cortical areas. Neuron-resolution studies, however, often target focal regions of cortex. As a result, we do not yet have a full picture of how movement-related information is spatially distributed among neurons across frontal motor areas and cortical layers. We leveraged high-density laminar probes and largescale implants to examine how movement information is distributed across multiple frontal motor cortical areas.
We recorded neural activity at locations distributed across dorsal premotor cortex (PMd) and primary motor cortex (M1) while one rhesus macaque (male, 11 years old) performed a center-out reaching task. The monkey's arm movements controlled a cursor on a screen as they made reaches to eight different targets. Our neural implant approach leverages a design that allows flexible access to a 2-centimeter diameter window over the cortical surface. We inserted high-density, laminar, microelectrode arrays (Neuropixels) at locations across the implant window to compare target information across the cortical surface at single neuron resolution across different cortical depths.
We used decoding analyses to reveal that target information was tightly clustered by the location of units across the cortical surface. This analysis revealed that a few 'high-decoding' sites significantly outperformed other sites. Notably, high-decoding sites were within millimeters of sites with significantly less target information. Unit-adding analysis further showed that units recorded at high-decoding sites each more strongly contributed to decoding compared to units recorded at the remaining locations. We also recorded surface potentials with a large-scale micro-electrocorticography (μECoG) array that spanned the chamber while the same monkey performed the same task. μECoG measurements revealed localized differences in movement-related information across motor cortex that correlated with the target information seen at the level of single neurons.
The distribution of target information at the single neuron level across the motor cortical surface highlights the potential importance of considering the spatial location of recorded neurons when investigating functionally defined networks across multiple areas. This may be especially important because our results also suggest that high-decoding sites are spatially precise, spanning only millimeters. This study also suggests the potential importance of combining data-driven sampling with population analysis to better understand motor encoding.

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Poster

PSTR120: Target-Directed Movement Control

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Support: Nakajima Foundation
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NIH BRAIN Initiative U01 (UF1NS126485)

Title: Gradient encoding of eye, hand, and target position in the motor cortex using a high density laminar probe

Authors: *T. OUCHI[1], R. CANFIELD[2], L. R. SCHOLL[1], A. L. ORSBORN[1,2,3];
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Abstract: We typically receive visual information through eye-centered coordinates, while motor output is processed via arm-centered coordinates. The dorsal premotor cortex (PMd) is involved in integrating both sets of coordinates. Previous studies have demonstrated that PMd encodes the positions of the hand, eye, and target (Pesaran et al. 2006; Batista et al. 2007). However, neural data at different locations within PMd and primary motor cortex (M1) were sparsely sampled and pooled together. Recent studies highlight that different types of task information are spatially organized within PMd and M1 (Nakayama et al., 2017; Chandrasekaran et al., 2017). We therefore explored the spatial organization of eye, hand and target positions in PMd using high-density laminar probes (Neuropixels) to sample neural activity at different locations within frontal motor cortices. We trained one male macaque monkey to perform a saccade task while controlling hand position. The monkey had to fixate an initial eye target and maintain the hand position within an initial hand target during the delay period (400 ms - 700 ms). He then had to generate a saccade to an eye target while maintaining his hand position. We recorded spiking activity of neurons using a Neuropixels probe targeted to PMd and M1 (N=82, 132, 55, 46 neurons for 4 recording sessions). Neural data was analyzed across 27 conditions (three initial hand positions, three initial eye positions, and three eye targets) to assess information about each effector and targets. We quantified information about each effector and targets using linear discriminant decoding analysis. The average firing rate during the delay period was used to predict the three initial hand positions, three initial eye positions, or three eye targets, independently. Then, the decoding accuracy was calculated for each neuron. Our result revealed the presence of neurons encoding initial eye positions, initial hand positions, or eye target positions in all recording sites. Moreover, the proportion of eye-encoding neurons decreased as the recording location was shifted more caudally (towards M1). These results reveal a spatial gradient of arm and eye/target information within PMd. Our study highlights the importance of spatial mapping within frontal motor cortices and open avenues to explore computational transformations occurring within and across cortical areas.

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Poster

PSTR120: Target-Directed Movement Control

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Support: Eric P. and Evelyn E. Newman Fund

Title: The Synergy Expansion Hypothesis

Authors: *F. TESSARI, A. M. WEST, Jr., N. HOGAN;
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Abstract: Despite the heroic efforts of the research community, human motor coordination still represents an intriguing and open challenge. Several theories were proposed to explain how we, humans, manage to control the astonishingly large number of degrees of freedom of our musculo-skeletal system. The theory of motor synergies appears as one possible answer to this open question. In the motor control literature, motor synergies are presented as a way to reduce control complexity by using lower dimensional subspaces. Synergies are typically extracted using dimensionality reduction techniques e.g., PCA, NNMF or SVD, on human behavioral data either at the kinematic or muscular level. Evidence of dimensionality reduction was found at all levels, thus suggesting that humans might employ such lower dimensional commands to simplify motor coordination. However, not much investigation has been done on the nature, use and evolution of motor synergies. Here we present a new theoretical framework that aims to answer the following questions: (i) What is the maximum and minimum number of synergies that humans can have? (ii) How do humans develop and learn synergies throughout their life? (iii) How do humans make use of motor synergies? The proposed theoretical framework is named the "synergy expansion hypothesis" and is organized as three propositions: mechanical, developmental, and behavioral. The mechanical proposition looks into the biomechanics of human motion and, specifically, in the role of geometry when moving between muscle, joint and task spaces. The developmental proposition dives into the literature on motor learning of infants and children to observe the emergence of a coordination-to-individuation gradient that can explain the evolution of motor synergies. The behavioral proposition provides a control framework to explain how synergies may be recruited during a specific motor task. A numerical simulation - based on a simplified human arm model - is used to clarify these propositions, with a particular emphasis on the application of the mechanical and behavioral claims. The synergy expansion hypothesis is reviewed in light of the existing literature on motor synergies, as well as with respect to other leading theories on human motor coordination. This new theory provides the basis for a novel and testable framework to improve our understanding on the nature, use and evolution of human motor coordination.

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Poster

PSTR120: Target-Directed Movement Control

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Title: Electrocorticography (ECoG) Reveals Rotational Dynamics of the Frontoparietal Cortex during Reaching in Non-Human Primates

Authors: *H. NAKAMURA, T. TAKEI;
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Abstract: Recent studies have revealed the presence of strong rotational dynamics in the neural population activity of the motor cortex during reaching movements in non-human primates, suggesting that the motor cortex functions as a dynamical system rather than a representation of movement parameters. However, it remains unclear whether these rotational dynamics can be observed using local field potential (LFP) recordings from electrocorticography (ECoG) electrode arrays. ECoG is a promising recording technique that provides stable, long-term recordings with high spatial resolution, covering large cortical areas. These characteristics make ECoG an attractive option for brain-machine interfaces (BMIs) and neuroscientific research. Demonstrating the presence of rotational dynamics in ECoG recordings would not only validate the findings from single-unit recordings but also open up new possibilities for translational applications and further our understanding of the motor cortex's functioning as a dynamical system. In this study, we investigated the population dynamics of LFPs recorded from ECoG arrays subdurally and chronically implanted on the frontoparietal cortical areas of two Japanese macaques (*Macaca fuscata*), during reaching movements. Specifically, ECoG arrays cover the primary motor, premotor, primary somatosensory, and posterior parietal cortex. We applied the jPCA method, which was previously used to identify rotational structure in single-unit recordings, to the LFP data. To incorporate the frequency-dependent temporal dynamics of the LFP signals, we computed the power of LFP signals in eight frequency bands (0.5-4 Hz, 4-8 Hz, 8-12 Hz, 12-25 Hz, 25-50 Hz, 50-100 Hz, 100-200 Hz, and 200-400 Hz) and the local motor potential. Our results reveal that the frontoparietal LFPs exhibit consistent rotational dynamics

during reaching, similar to those observed in single-unit recordings from the motor cortex. These findings demonstrate that LFP recordings using ECoG arrays can capture the essential population dynamics of the motor cortex, and can be a huge step forward for translational application. Additionally, this study highlights the potential of using ECoG arrays to uncover the complex interactions between the neural oscillations in the frontoparietal cortical network in the control of movement.

Disclosures: H. Nakamura: A. Employment/Salary (full or part-time):; Ruten Inc. **T. Takei:** None.

Poster

PSTR120: Target-Directed Movement Control

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Title: Different specialization for spatial and temporal reaching parameters across the medial fronto-parietal network of the macaque.

Authors: *M. DE VITIS, M. FILIPPINI, K. CHATZIDIMITRAKIS, F. E. VACCARI, S. DIOMEDI, M. GAMBERINI, M. GORI, M. TESTA, C. GALLETTI, P. FATTORI;
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Abstract: Neuronal populations in the parietal and frontal cortices orchestrate a series of visuomotor transformations that are crucial for executing precise reaching movements. The medial sector of the fronto-parietal network is characterized by strong reciprocal connections between the dorsal premotor cortex (area F2), and the medial parietal area V6A. Despite extensive research, primarily focusing on center-out reaches without accounting for reach depth, a direct comparison of how various spatial and movement parameters are represented across different network nodes remains elusive. More specifically, it is unknown whether spatial variables like reach direction and depth are similarly encoded in frontal and parietal cortex and whether there are differences in the temporal evolution of activity that reflect functional specializations. To fill this gap, we trained *Macaca fascicularis* monkeys to perform an instructed delay reaching task towards targets located at different directions and depths within the peripersonal space. Spiking activity was recorded from 95 V6A neurons and 75 F2 neurons, and analyzed during different phases of the task, including reaching preparation (PLAN) and execution (MOV). Overall, in the vast majority of neurons (96% in V6A and 99% in F2) neural activity was modulated in at least one of the task epochs compared to the baseline activity (t-test,

p<0.01). To quantify the strength of modulations along direction and depth dimensions, we calculated a spatial preference index by contrasting the average activity for the left/right positions in direction and near/far positions in depth. V6A showed strong spatial modulations during MOV, with a wide index distribution for both direction (mean ± SD: 0.29 ± 0.26) and depth (mean ± SD: 0.33 ± 0.27). In contrast, F2 exhibited weaker tuning for spatial parameters, with a narrow index distribution centered around 0 (mean ± SD: 0.1 ± 0.1 for both direction and depth). Interestingly, F2 showed a more pronounced difference in activity between movement planning and execution phases (78% of the F2 population compared to 19% of V6A, PLAN vs. MOV, t-test p<0.01), indicating a significant transition in neural dynamics. Our results highlight a pronounced specialization of spatial and temporal movement parameters across key nodes of the fronto-parietal network, with parietal area V6A exhibiting stronger spatial tuning and frontal area F2 showing distinct neural dynamics during reaching.

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Poster

PSTR120: Target-Directed Movement Control

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Title: Independent encoding of grasping type and force in the primate motor cortex

Authors: *A. MORENO[1,2], V. DE LAFUENTE[2], H. MERCHANT[2];
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Abstract: It is well known that the primary motor cortex (M1) has a causal role in motor execution. However, the exact mechanisms by which M1 controls movement are still not well understood. Neural responses in M1 are evoked during both planning and movement execution and have shown to be heterogeneous. Most studies have focused on the executive aspects of motor control; however, evidence suggests that M1 neural activity can also represent abstract external and internal parameters such as deliberation signals and motor context. Such representations are essential for appropriate action selection and execution. The aim of our study was to determine how movement parameters that are relevant for task solving are represented in the neural activity of M1, especially during motor planning. To do this, we analyzed neural data previously published by Brochier et al. (2018). This database included neural recordings from

M1 of two monkeys performing a delayed reach-to-grasp task. In this task, animals were trained to grasp an object using either a side or a precision grip, and then pull it with a low or high force level, depending on trial condition. The task design allowed the study of grip planning and execution separately, while both processes where temporally overlapped in the case of force level. M1 neural activity contained significant amounts of mutual information related to the main task parameters: grip and force. Grip was more prominently represented than force and this representation emerged during the preparatory period of the task. Remarkably, encoding of grip and force in M1 was carried by overlapping neural subpopulations in a categorical manner, in which both parameters showed to be independently encoded at single-cell and population levels. Population-level representation of both parameters allowed to decode task conditions of single trials. Furthermore, cross-temporal decoding analyses revealed that grip encoding followed a temporally stable coding scheme, while force was dynamic. This revealed the presence of a flexible coding scheme in M1 that adapts to task demands. Taken together, our findings demonstrate that M1 neural activity represents grip and force independently and that the coding scheme of these parameters adapts to the time available for their preparation. This contributes to the view that task-relevant movement parameters may be represented abstractly in M1, similarly to other motor-planning and associative areas such as the prefrontal and premotor cortices.

Disclosures: A. Moreno: None. **V. de Lafuente:** None. **H. Merchant:** None.

Poster

PSTR120: Target-Directed Movement Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.09/D44

Topic: E.04. Voluntary Movements

Support: NIH/NEI RO1 EY024056

Title: A new principle in the kinematics of the neural control of hand movements during memory-guided drawing

Authors: *L. LIKOVA[1], K. MINEFF[1], M. LIANG[1], C. W. TYLER[2];
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Abstract: Introduction. The underlying principles of the neural control of human arm movement kinetics are now broadly understood to be governed by a power-law relationship between the speed and the curvature of the motion trajectory, which can be derived from the Minimum Jerk Principle of maximizing the smoothness of the motion. We asked whether the same principles operate during human drawing movements for the task of drawing from memory without visual feedback. Methods. The study was conducted in two groups of participants: completely blind, and sighted but temporarily blindfolded; deriving from studies of the effects of the Likova Cognitive-Kinesthetic Memory-Drawing Training, which is a rapid training procedure designed

to enhance spatial memory for both visually impaired and sighted people. The drawing trajectories were recorded during functional Magnetic Resonance Imaging (fMRI) scans of the cortical plasticity underlying the pronounced training effects on spatial memory and precise spatiomotor control. Post-training kinematics of drawing of the remembered trajectories were recorded on an MRI-compatible recording tablet for 12 drawings per participant. The velocities as a continuous function of local radius of curvature along the complex drawing trajectory were fitted with candidate forms of the power-law relationship. Results. The analysis shows that the Viviani-Flash model of arm-motion kinematics as a simple 1/3 power relationship of drawing speed to the local curvature of the line being drawn, as predicted from the Minimum Jerk Principle, is not a sufficient characterization of their coupling. Instead, the drawing dynamics conformed to a hyperbolic power relationship, with an approximately linear coupling power for regions of high curvature, asymptoting to curvature-independence for regions of shallow curvature. The power asymptote for regions of high curvature was significantly higher than 1/3, well beyond the range reported by previous studies of comparable angular curvature using visual feedback. Conclusions. The analysis reveals that the simple 1/3 power law for the neural control of hand velocity relative to the curvature of the drawing trajectory is an approximation to a more elaborate principle of a hyperbolic saturation function. For drawing without visual feedback the power asymptote of this new hyperbolic velocity/curvature function was substantially greater than the predicted 1/3 value.

Disclosures: L. Likova: None. **K. Mineff:** None. **M. Liang:** None. **C.W. Tyler:** None.

Poster

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Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant RGPIN-2023-05273

Title: What's touch got to do with musicians' motor performance: the interaction between tactile suppression, expertise and difficulty in piano key presses

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Abstract: In a noted paradox, while tactile inputs are crucial for motor performance, tactile perception is suppressed across movement contexts. A much-cited factor in tactile suppression is input predictability. We previously found that expert pianists, despite having strong predictive internal models for piano key movement, do not show more tactile suppression than untrained participants in a piano key press. These findings suggest another factor influencing tactile suppression: i.e., task relevance.
Our present study tested tactile suppression in piano key presses of increasing difficulty (i.e.,

slow velocity control). We hypothesized that expert pianists, through familiarity with the relevance of tactile inputs for velocity control, would showing less tactile suppression than untrained participants with this increased difficulty.
We tested 13 expert pianists (Expert: 7 female; *30.0y/10.8SD)* and 12 untrained participants (Untrained: 6 female; *26.7y/6.9SD).* Tactile perception was tested by presenting weak, variable intensity electrical currents to the skin at 3 timepoints (Baseline, at rest; P: Planning, 350 ms before key press; E: Execution, synchronous with key press) measured in 3 movement blocks of varying difficulty: unspecified speed, no sound (Control); slow (>100 mm/s) no sound (SlowNS); slow with sound (SlowS). Threshold was defined as the intensity level at which 50% of stimuli were perceived. Suppression in planning and execution were measured as threshold differences with baseline, and were derived for each difficulty level: planning and execution suppression Control (P-Control, E-Control), SlowNS (P-SlowNS, E-SlowNS), SlowS (P-SlowS, E-SlowS).
A repeated measure ANOVA of planning suppression, 2 group (Expert, Untrained) by 3 difficulty (P-Control, P-SlowNS, P-SlowS) showed a main effect of difficulty ($f(2,46)=8.81$, $p<.001$), no main effect of group ($p=.16$), and no interaction ($p=.83$). Post-hoc t-tests showed more planning suppression in slow key presses: SlowNS v Control: $t(24)=2.87$, $p=.008$; SlowS v Control: $t(24)=3.48$, $p=.002$.
A repeated measure ANOVA of execution suppression, 2 group by 3 difficulty (E-Control, E-SlowNS, E-SlowS), showed a main effect of difficulty ($f(2,46)=17.40$, $p<.001$), no main effect of group ($p=0.85$), and no interaction ($p=.98$). Post-hoc t-tests showed less execution suppression in slow key presses: SlowNS v Control: $t(24)=-6.24$, $p<.001$; SlowS v Control: $t(24)=-3.74$, $p=.001$. All t-tests were Holm-Bonferroni corrected.
These findings on interactions between task difficulty, movement phase and tactile suppression further our understanding of tactile perception's role in expert motor control.

Disclosures: J. Tom: None. **J.L. Chen:** None.

Poster

PSTR120: Target-Directed Movement Control

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Program #/Poster #: PSTR120.11/D46

Topic: E.04. Voluntary Movements

Support: Canada First Research Excellence Fund (CFREF)

Title: Ventrolateral Prefrontal Cortex activity during a head unrestrained, memory guided reach task

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Abstract: In a previous study, we identified a region in the posterior-lateral prefrontal cortex that codes gaze, head, and hand movement signals during head-unrestrained reaches in Rhesus macaques (Nacher et al., Society for Neuroscience Abstract 2022). The purpose of the current study is to investigate how the population activity of groups of neurons in the posterior ventral prefrontal cortex (pVLPFC) is modulated during a more complex, memory-guided reach task. We implanted a 128-channel Plexon Array over the pVLPFC. Single unit activity and LFPs were recorded simultaneously in a female Rhesus monkey trained to perform a memory-guided reaching task. The hand was initially placed at 1 of 3 varying locations of a waist level LED bar while gaze fixated centrally. A landmark was presented at 1 of 15 locations on a touch screen. A visual target then appeared transiently at a variable location within or outside this virtual square, followed by a visual mask. After the mask, the landmark either reappeared at the same location (stable landmark condition) or shifted by 8 degrees in one of 8 directions (landmark shift condition). The fixation light then extinguished, signaling a reach to the target. 'No-landmark' controls were the same, but without the landmark. Neural and behavioral (eye, head, hand) signals were then recorded daily for four months while the animal performed this and other related tasks. In general, gaze shifts were followed by head motion and reasonably accurate hand motion, but gaze was less locked to the target and hand position after a memory delay compared to a visually guided reach task (Lin et al., Society for Neuroscience Abstract 2022). We are currently analyzing LFPs to determine how they are modulated by different time points of the task. We are expecting to observe modulations in oscillatory activity comparing the task conditions (landmark stable, shifted and no-landmark).

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Poster

PSTR120: Target-Directed Movement Control

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.12/D47

Topic: E.04. Voluntary Movements

Support: NIH Grant 5R01NS118030-03
HFSP LT-0030/2022

Title: Somatosensory cortex supports rapid integration of tactile feedback during a dexterous reach-to-grab motor task

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Abstract: Sensory feedback is critical for skilled motor actions performed by the mammalian motor system. Tactile inputs provide information about interactions in the environment such as whether an effector has come into contact with an object of interest or has missed the object requiring a corrective action. Rapid integration of tactile inputs with ongoing motor actions is believed to be supported by the hand subdivision of primary somatosensory cortex (S1hand). However, most studies of S1 have focused on its role in tactile perception or focused on corrective motor actions generated by proprioceptive feedback rather than tactile feedback. Here, we examined the role of S1hand in mice trained to reach out and grab for food pellets following an auditory cue (reach-to-grab task). Mice initiated the reaching movement by lifting their paw from the perch ~200-300ms after the arrival of the cue and would contact the pellet ~50-100ms after the lift. We recorded spiking activity from S1hand using neuropixel probes (4 mice, 431 neurons). S1hand activity tiled the entire reach behaviour, however neuron activities tended to peak around when the pellet was grabbed rather than other behavioural events (e.g. lift or cue). Neuron activities also exhibited larger peak firing rates when aligned to the grab event versus when aligned to the lift or cue suggestive of a preferential role in encoding the grab event. Contrasting grab attempts that were successful (i.e. grabbed the pellet) with failure (i.e. missed the pellet) revealed that S1hand activity differentiated between these grab types within ~20ms after the initiation of the grab indicating a rapid transmission of tactile information. Next, we sought a causal role of S1hand in the reach-to-grab task by optogenetically silencing S1hand. On control trials, mice grabbed the pellet successfully on their initial attempt in approximately 50% of the trials. Error trials where the initial grab attempt was unsuccessful was often followed by several re-attempts by the mice to grab the pellet. Comparing successful and failed reach attempts revealed differences in the kinematics that started to emerge ~100ms after the grab event. However, on trials where S1hand was silenced, kinematics did not differentiate between successful and unsuccessful reaches for >300ms after the grab event. Collectively, these results highlight how rodent S1hand supports rapid tactile integration for ongoing motor actions.

Disclosures: K. Cross: None. **A.W. Hantman:** None.

Poster

PSTR120: Target-Directed Movement Control

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.13/D48

Topic: E.04. Voluntary Movements

Support: NIH P51OD010425

Title: Developing an automatic in-cage touch screen system to optimize high throughput experiments in non-human primates.

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Abstract: Neuroscience research in non-human primates is traditionally conducted in controlled lab environments where we can systematically manipulate behavior and perform detailed neurophysiology. Lab-based experiments often introduce time-consuming and costly additional steps before any data collection can begin. These additional steps can serve as bottlenecks in experiment pipelines that severely limit the number of animals that can be studied for a scientific question.

Performing experiments within the animal's home cage ("in-cage") provides alternative ways to collect data without significant additional non-task-related behavioral training. Many studies leverage in-cage experiments to perform high-throughput behavioral and neurophysiology studies in rodents (e.g., Poddar et al 2013). In-cage training has also been used in non-human primates with a focus on decreasing task-training times (e.g., Griggs et al 2021). Here, we focus on developing automated in-cage behavioral tasks for non-human primates with a goal of enabling high throughput studies of rich motor behaviors.

Towards our goal of collecting data from tens of animals, we developed a customizable, low-cost, open-source, in-cage touch screen tablet interface that can be scaled up to run multiple animals simultaneously. We centralized running the experimental software onto a 'home computer' that can run tasks locally and then stream task stimuli remotely to the in-cage tablet via a secure intranet. This allows multiple independent tablets to run experimental tasks simultaneously. After the startup cost of the home computer (~$2,000), additional setups are less expensive (~$1,000 each), including a tablet, pellet reward system, and mounting hardware.

We optimized our experimental design around a continuous tracking task where animals touch and follow the path of an oscillating target on the screen. Through only positive reinforcement training, we found that animals could perform sustained tracking tasks for upwards of 20 seconds.

We also aimed to streamline animal training to improve throughput. We developed an app to provide a visual dashboard of both recent and cumulative training sessions, as well as model-based predictions of a subject's future performance. The app also automatically selects training parameters using a novel reinforcement learning agent. The agent itself improves in its performance when using a simulator trained on data from many animals.

Together, this system makes it possible to efficiently run higher throughput experiments and keep track of individualized training in a more natural environment where the animals can freely engage with the motor control tasks.

Disclosures: L. Smith: None. **C. Rasgaitis:** None. **K.M. Perks:** None. **L.R. Scholl:** None. **A.L. Orsborn:** None.

Poster

PSTR120: Target-Directed Movement Control

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Program #/Poster #: PSTR120.14/D49

Topic: E.04. Voluntary Movements

Support: Jean Sheng
NSF Graduate Research Fellowship

Title: A collicular map for touch-guided tongue control

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Abstract: Accurate goal-directed behavior requires the sense of touch to be integrated with information about body position and ongoing motion. Behaviors like chewing, swallowing and speech critically depend on precise tactile events on a rapidly moving tongue, but neural circuits for dynamic touch-guided tongue control are unknown. Using high speed videography, we examined 3D lingual kinematics as mice drank from a water spout that unexpectedly changed position during licking, requiring re-aiming in response to subtle contact events on the left, center or right surface of the tongue. Mice integrated information about both precise touch events and tongue position to re-aim ensuing licks. Surprisingly, touch-guided re-aiming was unaffected by photoinactivation of tongue sensory, premotor and motor cortices, but was impaired by photoinactivation of the lateral superior colliculus (latSC). Electrophysiological recordings identified latSC neurons with mechanosensory receptive fields for precise touch events that were anchored in tongue-centered, head-centered or conjunctive reference frames. Notably, latSC neurons also encoded tongue position before contact, information important for tongue-to-head based coordinate transformations underlying accurate touch-guided aiming. Viral tracing revealed tongue sensory inputs to the latSC from the lingual trigeminal nucleus, and optical microstimulation revealed a topographic map for aiming licks. These findings demonstrate for the first time that touch-guided tongue control relies on a collicular mechanosensorimotor map, analogous to collicular visuomotor maps associated with visually-guided orienting across many species.

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Poster

PSTR120: Target-Directed Movement Control

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Program #/Poster #: PSTR120.15/D50

Topic: E.04. Voluntary Movements

Support: Pennsylvania HRFG

Title: Neural state transitions in the motor cortex during reaching

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Abstract: Single-unit firing rates in the motor cortex (M1) can be multiphasic during straight arm reaches. This cannot be explained by the classic directional tuning model which would predict a single epoch of firing rate modulation. A recent dynamical systems model attributed neural dynamics during reaching only to intrinsic neuron-neuron interactions in M1. However, new evidence challenged this perspective by showing that input from other brain regions was necessary for these dynamics to take place. Here, using two artificial neural network models and M1 neuronal activity, we show how dynamic input can drive multiple state transitions of neural population activity during reaching.Two rhesus monkeys performed a standard center-out reaching task while neural activity was recorded from M1. Firing rates of individual simultaneously recorded neurons were calculated for 16 movement directions. Dimensionality reduction was performed to find a 6-dimensional feature space that captured about 70% variance of the neural population activity. A rotation of this feature space yielded three 2-dimensional neural activity planes. Each plane represented a unique neural state and these three neural states emerged sequentially in different epochs of reaching. We hypothesize that these transitions of neural population activity are driven by external inputs that reflect evolution of motor demands as movement unfolds.We first modeled inputs as three pairs of direction-tuned signals that linked respectively with three behavioral events: movement onset, peak speed and movement offset. With these inputs, a recurrent neural network (RNN) was trained to replicate recorded neuronal firing rate profiles. The RNN reproduced recorded neuronal activity with high fidelity. An analysis of state-space trajectories revealed that the three pairs of inputs drove RNN state through three subspaces sequentially and yielded trajectories like those observed in motor cortex. We further tested this idea with a spiking neural network (SNN). Three groups of input neurons firing episodically during the reach were used to drive the firing rates of output neurons representing the units recorded experimentally. All inputs were connected to all output units. Synaptic weights were learned from input and output spike trains following the Hebbian rule. The predicted output activity, driven solely by the input spike trains, matched that of the recorded motor cortical neurons reasonably well. Results from both network models show that dynamic, behavior-related changes in the active input repertoire to each output neuron can drive state transitions in M1 populations during reaching.

Disclosures: H. Mao: None. **B. Hasse:** None. **A. Schwartz:** None.

Poster

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Ministry of University and Research PRIN 2022 (22SP5K99) to Monica Maranesi

Title: From walking to reaching: single neuron and population dynamics in monkey lateral frontal cortex

Authors: *R. SINI[1], D. ALBERTINI[1], F. LANZARINI[2], F. TILI[3], M. MARANESI[1], L. BONINI[1];
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Abstract: Walking and reaching behaviors have been traditionally investigated as separate motor functions due to their distinct motor patterns and neural substrates. While walking entails coordinated movements of the entire body for navigation and environmental exploration, reaching involves precise forelimb actions aimed at grasping and manipulating objects. Walking has been extensively studied by focusing on the central pattern generators in the spinal cord and the contributions of the medial primary motor cortex, while the neural bases of reaching have been investigated at the level of parieto-frontal cortical circuits of the lateral reaching-grasping network. However, both walking and reaching require precise spatial positioning of the limb, suggesting a potential functional and evolutionary link between their cortical substrate. Here, we explored this link by conducting wireless neural recordings with chronic microelectrode arrays implanted in the left lateral frontal cortex of two freely moving rhesus macaques. Within a large plexiglass enclosure, the monkeys were free to spontaneously walk and catch food hanging from the ceiling or grasp it from the floor, while being monitored by a multi-cameras system. We recorded 224 neurons, out of which 102 (45%) exhibited robust responses during walking. They displayed highly consistent, rhythmic firing patterns synchronized with specific phases of the step cycle, often in correspondence with the extension phase of the contralateral forelimb, just before ground contact. About 30% of all recorded neurons responded during the reaching phase of grasping actions, and a sizable fraction of them were similarly modulated across both walking and reaching. Finally, electrical microstimulation applied to the channels hosting walking-and-reaching neurons provided causal evidence of their involvement in forelimb or axio-proximal movements, indicating the existence of a shared control for these behaviors. Together, these findings provide empirical support to the long-standing hypothesis of a common phylogenetic origin of the neuronal substrates involved in reaching actions from those originally devoted to the voluntary control of locomotion.

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Poster

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Title: Neuronal correlates of grip coding in freely moving monkeys

Authors: *F. CIMMELLI[1], M. MARANESI[2], L. BONINI[1];
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Abstract: The investigation of the cortical mechanisms for the organization of manual actions has emphasized, so far, the distal components of hand shaping and finger control for grasping as a distinctive feature of the ventral premotor cortex. An untested assumption of this view is that the selectivity of ventral premotor neurons for specific grip types remains unchanged when the same object is grasped from different spatial positions, and hence with different body postures, during unconstrained grasping actions. Here, we tested this prediction by recording single neuron activity from the ventral premotor cortex of two freely moving rhesus macaques with chronically implanted floating multielectrode arrays (128 ch). During the recordings, monkeys had to grasp the same two objects, a big and a small sphere, with a Whole Hand (WH) and Precision Grip (PG), respectively, while the targets were in different positions of the monkeys' home cage: on the floor, on a low or upper part of the cage wall, or on the ceiling. This placement of objects necessitated the monkeys to adopt different body postures to reach and grasp them: quadrupedal, sitting and facing downward, sitting and facing forward, standing and facing upward. We recorded 225 neurons, among which 28 did not show any modulation during grasping actions, whereas the remaining significantly modulated their activity during at least one grip type in at least one position (n=197). The fraction of modulated neurons was similar for all positions, considered separately, as well as the fraction of grip selective neurons. Some neurons (n=54) discharged without grip selectivity in all four positions, while, among grip selective neurons, virtually no one maintained the same grip selectivity when tested in different position: 2 neurons exhibited the same selectivity (PG) in 3 positions; 33 neurons maintained their selectivity for the big (n=10) or the small (n=23) objects in two positions; an even larger fraction (WH, n=39; PG, n=43) encoded the grip type in only one position, and a final set exhibited different grip tuning depending on the object location (n=26). Although preliminary, these results highlight the possible role of axio-proximal components as a powerful source of modulation for the encoding of distal parameter of hand shape for grasping.

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Poster

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Topic: E.04. Voluntary Movements

Support: UNAM-DGAPA-PAPIME PE205821 (RO-M)
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Cutberto Dorado
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Ericka de los Rios
Deisy Gasca
Martín García Servín

Title: Subtypes of pyramidal tract neurons in motor cortex participates differentially in a behavioral task of reaching movement.

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Abstract: The specific roles of distinct subtypes of pyramidal tract neurons (PTNs) in the sensorimotor cortex remain largely unknown. In this study, we examined the functional roles of two classes of PTNs: those projecting to the spinal cord (corticospinal tract neurons) and those projecting to the red nucleus (corticorubral tract neurons). Our aim is to characterize the involvement of these neural pathways in voluntary movement and determine whether they exhibit differential roles in the preparatory and execution phases of movement, as well as in specific forelimb movements. To achieve this, we conducted selective optogenetic inhibition experiments targeting sensorimotor cortex corticospinal (CST) or corticorubral (CR) neurons during reaching movement, analyzing the performance of rats trained in an operant conditioned task.
During the behavioral task, the rats learned to wait for a randomly time (500, 1000, 1500 ms) during the preparatory phase until a go cue signaled the start of the execution of the reaching movement, which allows us to separate both phases of the movement. During the training this movement became more precise and stereotyped over time. Consequently, through photoinhibition, we observed that CST and CR neurons play distinct roles in both the preparatory and execution phases, as well as in the movement of the fingers of the forelimb. These findings suggest that different subtypes of PTNs in the motor cortex exhibit specific and complementary roles for the preparation and execution phases of voluntary movements.

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Poster

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Program #/Poster #: PSTR120.19/D54

Topic: E.04. Voluntary Movements

Title: Tdcs does not enhance motor skill acquisition in left-handed individuals

Authors: T. HERRIN[1], C. JONES[1], A. HELMS[1], J. BEANE[1], J. SENTMAN[2], ***L. LIMA DE ALBUQUERQUE**[3];
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Abstract: Transcranial direct current stimulation (tDCS) has demonstrated efficacy in enhancing motor skill acquisition, particularly in simple hand and arm tasks. However, its effectiveness in improving performance in complex, whole-body coordination tasks remains uncertain. Furthermore, the limited research on tDCS effects in left-handed individuals, owing to their neurophysiological and anatomical variability, underscores the need for investigation in this population.This study aimed to investigate the impact of tDCS on motor skill acquisition in left-handed individuals performing an overhand throwing task. Employing a randomized, SHAM-controlled, within-participants, double-blind design, 12 participants completed both tDCS and SHAM conditions across two sessions separated by a 7-day washout period. During each session, participants engaged in overhand throwing practice to a designated target 6 meters away using their non-dominant hand. The protocol comprised seven trial blocks, including baseline, practice, and post-test blocks, with a retention test block conducted 24 hours later. Anodal tDCS was administered over the left motor cortex targeting the first dorsal interosseus (FDI) muscle representational area during practice sessions for 20 minutes. The stimulation parameters (current strength: 1 mA; anode: FDI; cathode: contralateral supraorbital area) were based on established effective settings. tDCS was delivered via a NeuroConn Stimulator stored in a non-restrictive backpack.Motor performance was assessed by measuring endpoint error, defined as the absolute distance between the final position of the ball and the target center. Both groups demonstrated a reduction in endpoint error from baseline to post-test blocks, indicative of motor learning. However, no significant differences or interactions between groups were observed (all $p > 0.2$), suggesting that a single session of tDCS did not enhance motor learning in complex overhand throwing tasks among left-handed young adults.These preliminary findings underscore the need for further investigation into the effectiveness of tDCS protocols in enhancing motor skill acquisition in diverse populations and complex motor tasks.

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Poster

PSTR120: Target-Directed Movement Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.20/D55

Topic: E.04. Voluntary Movements

Support: NSF EFRI BRAID 2223822

Title: Evaluating geometric similarity between neural activity and behavior using multi-level representational similarity analysis

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Abstract: Population-level neural activity across time can be represented as a trajectory on a neural manifold. As neural circuits have evolved to be efficient, we hypothesize that similarity in the neural population activity (neural trajectories) across conditions/trials implies similarity in the behavior executed. To study this, we present an unsupervised approach to determine the relation between the geometry of neural activity and behavior. Specifically, we introduce a multi-level Representation Similarity Analysis (RSA) metric and present results on neural & behavioral data obtained from non-human primates performing hand-reach tasks in 108 different maze settings [Churchland et al. 2012]. In the neural domain, we apply hierarchical clustering using pairwise distances between neural trajectories and organize the corresponding behaviors based on the resulting dendrogram. At every node in the dendrogram, we calculate the similarity between the neural activity and behavior distance matrices using RSA, considering only the conditions/trials (root nodes) that are clustered under that node. We used data comprising simultaneous recording of neural activity (137 neurons in primary motor cortex and premotor cortex) and the corresponding behavior (hand velocity and position) obtained across 2295 trials. We performed this analysis on both trial-averaged data and single-trial data. Single-trial analysis allowed the introduction of complexity in the data due to inherent variability in behavior and neural activity. The results obtained remained consistent across both single-trial and trial-averaged analysis. Our approach identified that similar neural activity corresponds to hand reaches that are similar to each other and also grouped reaches made to similar targets together. The RSA between the neural activity and behavior decreased as we traversed higher and higher nodes in the dendrogram. At the lower nodes the RSA values were closer to 1 in both single-trial and trial-averaged analysis, and at the root node, the RSA values were 0.52 and 0.68 respectively. We also noted that the RSA between the neural activity and hand velocity was consistently higher than that between neural activity and hand position. This confirms with the observation that motor cortical activity correlates better to velocity than position during arm movements. Our approach provides a framework for analyzing and quantifying the relationship between the geometry of neural activity and behavior using multi-level RSA, and a principled approach to evaluate neural latent representations and identify ones that best captures the similarity between the neural activity and behavior.

Disclosures: S. Narasimha: None. **J. Huang:** None. **V. Gilja:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified

mutual funds); Shareholder in Neuralink Corp., Options holder at Paradromics, Inc.. F. Consulting Fees (e.g., advisory boards); Chief Scientific Officer at Paradromics, Inc.. **G. Mishne:** None.

Poster

PSTR120: Target-Directed Movement Control

Location: MCP Hall A

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Program #/Poster #: PSTR120.21/D56

Topic: E.04. Voluntary Movements

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 425899996

Title: Can we learn while doing nothing? - A probe into 'offline learning' in early motor skill acquisition in humans

Authors: *A. DAS[1,2], A. KARAGIORGIS[3,2], J. DIEDRICHSEN[4], M.-P. STENNER[5,6], E. AZAÑÓN[7,2,6];
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Abstract: Learning of a novel skill occurs by fast improvements in performance, exhibited generally during practice (online learning) and also across rest (offline learning). Previous research has suggested a form of offline learning for motor sequences, evidenced by performance improvements across short 10 s breaks (‘micro-offline gains’, MOG), which correlated with temporally compressed sequence-specific neural replay detected in rest-period MEG signals. Our hypothesis was that if people indeed ‘learnt offline’, they should acquire a higher skill level i.e. exhibit better performance, when training with vs. without breaks. Healthy human participants trained to produce a sequence of five keypresses as often as possible in 10 s practice periods with interspersed 10 s rest periods. In three experiments (in-lab N=62 & N=85; crowdsourced N=358), we observed significant MOG in the group ‘with breaks’, yet they performed comparable number of correct keypresses as a control group which trained without breaks, when tested after a longer retention period. Thus, we found no overall learning benefit whether humans trained with or without interspersed offline periods. Next, to investigate whether replay is necessary for MOG, we ran two between-subject studies (with & without advance information during rest, N=43 & N=35). One group of participants performed a fixed sequence which repeated in every practice period and another group performed novel, never-repeating sequences throughout the entire experiment, preventing them to benefit from replay of any previously encountered sequence. We found similar MOG when participants performed sequences that

never repeated, questioning a role of replay in driving these improvements. However, MOG in the 'non-repeating' group were significantly smaller when there was no advance information and the rest could not be used to prepare for an upcoming practice period. Therefore, we investigated motor planning as a factor in driving the performance improvements, and observed significant reduction of MOG (N=35) when participants could plan only one future finger movement at a time compared to five future movements. Moreover, we detected a planning gradient of finger movements in MEG data (N=30) right before movement initiation in a practice period, which can potentially be a metric of the extent of pre-planning. Overall, our data indicate that MOG during breaks are transient performance boosts, which do not reflect true 'offline learning', and are driven by the possibility to pre-plan, among other factors. Our findings can help inform strategies that benefit early motor skill acquisition in humans.

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Poster

PSTR120: Target-Directed Movement Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR120.22/D57

Topic: E.04. Voluntary Movements

Support: NIH R01NS120226-01A1

Title: Evidence of reticulospinal modulation when opening the hand during shoulder abduction

Authors: *E. N. A. ADJEI[1], K. WRIGHT[2], J. P. DEWALD[3], J. YAO[4];
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Abstract: Despite the reticulospinal tracts' (RST) involvement in both proximal and distal upper limb control, they primarily facilitate gross movements. Such movements are characterized by extensive muscle coactivation with a flexion bias, as observed during tasks like shoulder abduction. This inherent flexion bias suggests that the RSTs may not allow for effective hand opening during shoulder abduction. Moreover, corticofugal projections to the reticular formation—the origin of the RSTs—provide the anatomical basis for RST modulation depending on task demands. Therefore, we investigated how the RSTs are modulated when opening the hand while abducting the shoulder (LIFTOPEN task). To investigate RST modulation, we used the startReact paradigm. This method is characterized by the rapid involuntary release of a planned movement, upon a startling acoustic stimulation (SAS), mediated by the RSTs. We anticipate that in a shoulder abduction (LIFT) task, with increasing shoulder abduction load, there will be an increase in RST use, indicated by an increase in coactivation between the shoulder abductor and wrist flexor during startReact. However, as shoulder abduction load increases, we hypothesize that when there is a need to open the hand while lifting (LIFTOPEN),

the RSTs will be suppressed, reflecting cortical modulation of RSTs' use to combat the flexion bias. To test this hypothesis, we recruited 18 right-handed participants with no neuromuscular disorders. Using their dominant (right) arm, they performed LIFT and LIFTOPEN tasks at 25-53% of their maximum shoulder abduction force, in response to a SAS at 120 dB. During these tasks, we recorded electromyography from the right shoulder abductors, wrist and finger flexors and extensors as well as the bilateral sternocleidomastoids. Consistent with our hypothesis, our results revealed that with increasing shoulder abduction load, there was a significant decrease in shoulder abductor-wrist flexor coactivation during startReact in the LIFTOPEN task compared to the LIFT task. Importantly, this decrease in coactivation during LIFTOPEN was not attributed to reciprocal inhibition resulting from hand opening, as no negative correlation was observed between the wrist extensor and flexor activation. Our findings show that, when there is a need to open the hand while shoulder abducting, RST use is suppressed, providing evidence of RST modulation to optimize neural control based on task demands.

Disclosures: E.N.A. Adjei: None. **K. Wright:** None. **J.P. Dewald:** None. **J. Yao:** None.

Poster

PSTR120: Target-Directed Movement Control

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Program #/Poster #: PSTR120.23/D58

Topic: E.04. Voluntary Movements

Support: NIH R01NS120226-01A1
Sensorimotor Neurorehabilitation Training Grant

Title: Reticulospinal Engagement Increases As a Function of Shoulder Abduction Load

Authors: *K. M. WRIGHT, E. N. ADJEI, J. P. DEWALD, J. YAO;
Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL

Abstract: Much of what we know about the reticulospinal tract (RST) in humans has come from post-hemiparetic stroke studies. Direct , as recording of RST presents an obvious challenge in human study participants due to its location in the brainstem. As a result, little is known about how the cortex modulates the recruitment of the RST to select descending pathways in able able-bodied individuals. This study examines how whether RST engagement changes as shoulder abduction load increases during shoulder abduction (SABD) in a neurologically intact population. We hypothesize that lifting the arm against an increased shoulder abduction load increases the engagement of the RST as evidenced by an increase in coactivation between shoulder abductors and distal flexors.
To test this hypothesis, we recruited 25 right-handed neurologically intact participants to perform SABD over five different shoulder loads (25-53% of the participants' maximum voluntary SABD force). Each SABD load was assigned to a separate block of trials. All trials began with an 80 dB 'warning' cue, which instructed study subjects participants to begin preparing to self-

initiate SABD in 5 s. For 90% of all trials, a 2nd sound cue would be delivered 0.5-3.5 s prior to self-initiation. Subjects were instructed to release their prepared SABD as quickly as possible after hearing the 2nd sound cue. This 2nd sound was either an 80 dB 'go' sound (67% chance) or a 120 dB startling acoustic stimulus (SAS) sound (33% chance). Electromyographic data signals were recorded from anterior and intermediate deltoid, wrist and finger flexors and extensors, and the left and right sternocleidomastoid (SCM). Coactivation was calculated as muscle's activity divided by the sum of shoulder muscle activity. SAS trials were separated into 'startle response positive' (SR+) and 'startle response negative' (SR-) based on reaction time and SCM activity. We used a linear mixed effect model to test our hypothesis that SABD load has a positive relationship with of coactivation for with distal flexors. Our model had coactivation as an outcome measure, with trigger condition (Go, SR-, SR+), SABD load, and muscle group (flexor, extensor) as the fixed effects and included participant and muscle as random effects. We found that with increasing SABD load, there was an increase in shoulder abductor to with flexor coactivation ($p < 0.001$) during (SR+) trials. This finding supports our hypothesis that RST engagement increases as shoulder abduction load increases during SABD. This novel approach has given us insight into how descending pathway engagement changes with as a function of postural motor demands in able-bodied individuals.

Disclosures: K.M. Wright: None. **E.N. Adjei:** None. **J.P. Dewald:** None. **J. Yao:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.01/D59

Topic: E.07. Rhythmic Motor Pattern Generation

Support: National Science Foundation IOS 1755423

Title: Exploring the neural basis of behavioral evolution through computational modeling

Authors: L. BINDER[1], C. L. BARKAN[2], *E. ZORNIK[3];
[1]Biol., Reed Col., Portland, OR; [2]Biol., Williams Col., Williamstown, MA; [3]Reed Col., Portland, OR

Abstract: How do neuronal circuits produce synchronous activity over multiple timescales? In male *Xenopus* frogs, vocal circuits drive advertisement calls with temporal patterns that vary across species. Physiological studies have suggested that membrane and synaptic mechanisms underlie regulation of call timing. For example, high frequency spike synchrony appears to be a result of motor neuron driven inhibitory feedback, while call period may depend on calcium-activated potassium channels. To test whether variability in these and other mechanisms underlie species-specific call patterns, we modeled a *Xenopus* vocal circuit *in silico* using spiking neural networks. By generating large numbers of distinct networks across biophysically plausible parameter ranges, we identified circuit activity patterns that recapitulate the diversity of *Xenopus*

advertisement calls. Network simulations demonstrate the importance of inhibitory feedback; removal of inhibition disrupts spike synchronization without affecting slower bursting. Furthermore, a spike-dependent inhibitory conductance in premotor neurons - which replicates the activity of calcium-activated potassium channels - is necessary for producing stable, low-frequency periodic bursting. Slight modification of these parameters can lead to differences in call period that span ranges observed across species, in agreement with previous differential gene expression analysis. These results suggest that evolutionary changes in the expression of calcium-activated potassium channels and inhibitory feedback pathways may contribute to call period and spike synchronization differences across species. Taken together, our results demonstrate the utility of using computational modeling for investigating the neural mechanisms of behavioral evolution.

Disclosures: L. Binder: None. **C.L. Barkan:** None. **E. Zornik:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.02/D60

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01 NS104194
NIH R01 NS130799

Title: Phasic modulation of spinal deep dorsal RORB interneurons during locomotor-like activity

Authors: *C. WEST[1], D. GARCIA-RAMIREZ[2], K. J. DOUGHERTY[2];
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Abstract: Proprioceptive feedback to the nervous system is crucial for coordinated locomotion. During locomotion, sensory information continuously enters the spinal cord and may aid or perturb locomotion depending on when it occurs in the step cycle. GABAergic interneurons (INs) within a trisynaptic loop produce primary afferent depolarization (PAD), which strongly influences afferent transmission to locomotor circuits. Prior studies in decerebrated cats lacking sensory feedback have shown that the strength of PAD was dependent on the phase of ongoing fictive locomotion, suggesting that spinal locomotor circuit neurons may regulate sensory afferent feedback by modulating this trisynaptic loop. However, precisely if and how locomotor circuits provide phasic modulation to the PAD producing INs within the trisynaptic loop is unknown. Thus, we hypothesize that the GABAergic INs that produce PAD receive phasic modulation in the form of on-cycle excitation from spinal interneurons during locomotion. Here, we use male and female *RORβcre::R26-lsl-tdTomato* mice to identify RORβ INs in the medial deep dorsal horn, which have been previously shown to be GABAergic neurons that produce

PAD in proprioceptive afferents. Using a partial hemisection of the isolated spinal cord from neonatal (P2-P5) mice, we performed whole cell patch clamp recordings from visually-identified deep dorsal RORβ INs along with simultaneous ventral root recordings. During locomotor-like activity evoked by electrical stimulation of descending projections, we recorded postsynaptic currents, postsynaptic potentials, and action potential firing in RORβ INs which was examined in relation to activity in an ipsilateral flexor-dominant ventral root. We found that most RORβ INs receive phasic excitatory and/or inhibitory input and corresponding modulations in membrane potential related to ventral root bursting. These findings suggest phasic modulation of RORβ INs from multiple locomotor-related interneuron populations within the cord. Our results provide insight into a spinal mechanism mediating the phase-dependent control of proprioceptive afferent transmission during locomotion. As such, a greater understanding of the regulatory controls of afferent transmission may eventually be leveraged to improve sensory regulation and locomotor outcomes after SCI.

Disclosures: C. West: None. **D. Garcia-Ramirez:** None. **K.J. Dougherty:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.03/E1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council 2017-02905
Wallenberg Foundation KAW 2018.0010
Swedish Brain Foundation FO2021-0317
Karolinska Institutet

Title: Dual inhibitory speed-dependent circuits for locomotor coordination in adult zebrafish

Authors: *P. FONTANEL, L. D. PICTON, D. MADRID-PULGARIN, M. BERTUZZI, A. EL MANIRA;
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Abstract: Animals rely on locomotor flexibility to navigate their environment. In adult zebrafish, the spinal circuit organization for speed control is well-described and consists of three-speed modules composed of motoneurons (MNs) and ipsilateral excitatory interneurons (V2a INs) that are sequentially recruited to increase speed. However, the mechanisms underlying locomotor coordination across and along the body are still unclear. Recently, we revealed a similar modular organization in commissural inhibitory V0d INs alongside their role in maintaining coordination at slow speeds. In this study, we first characterized the function of a second population of inhibitory commissural interneurons, namely dI6 INs. We found that dI6 INs are predominantly recruited at fast locomotor speeds, as opposed to the V0d population exhibiting a bias toward slower speeds. Then, we tested whether V0d and dI6 INs are integrated

into the swimming circuit in a similar fashion and form a continuum to ensure coordination across all speeds. To address their pattern of connectivity within the locomotor circuit, we mapped the organization of the premotor drive from V2a INs to these inhibitory populations using dual patch-clamp recordings. We show strong and more frequent excitatory connections between V2a and V0d INs belonging to the same speed module. This circuit organization of premotor excitation mirrors the connectivity pattern observed with MNs, highlighting V2a INs pivotal role in synchronizing rhythmic output with the coordination across speeds. We are also assessing the ipsilateral drive to dI6 INs using a similar approach. Finally, we revealed connectivity from V0d and dI6 INs using optogenetic stimulation along the spinal cord combined with patch-clamp recordings. While both populations inhibit MNs, V2a INs, and homologs on the contralateral side, their organizations differ. V0d INs exhibit a neuron type-dependent pattern with strong long-range descending inhibition to MNs, a widespread inhibition to V2a INs with both long-range and local connections, independent of V0d IN position along the spinal cord, and local inhibition to contralateral V0d INs. In contrast, dI6 INs provided only local inhibition to contralateral MNs, V2a and dI6 INs. In summary, while V0d and dI6 INs share common features, they execute their functions with distinct patterns and speed preferences. This dual speed circuit may offer varying degrees of inter/intra-segmental control for proper coordination based on the locomotor speed.

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Poster

PSTR121: Interneurons and Motor Neurons

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Program #/Poster #: PSTR121.04/E2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: R01 NS104194
R01 NS130799
T32 NS121768
F31 NS135913

Title: Deep dorsal glycinergic interneurons that inhibit Shox2 interneurons overlap with molecularly-defined populations involved in sensorimotor function in the spinal cord

Authors: *J. R. MCGRATH, D. GARCIA-RAMIREZ, K. J. DOUGHERTY;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: A spinal cord injury (SCI) is a traumatic event that disrupts descending control of spinal circuitry, and often leads to severe locomotor deficits. Most SCIs occur at the cervical level, leaving the lumbar segments of the spinal cord below the injury relatively intact. This includes essential locomotor circuits that generate both the rhythm and pattern of locomotion.

These locomotor circuits are comprised of populations of spinal interneurons (INs) that can be characterized and identified by molecular markers. One such population is identified by the transcription factor Shox2 and is involved in both rhythm generation and pattern formation, providing a possible access point to control locomotor function. In an effort to improve locomotor recovery after SCI, rehabilitative strategies such as epidural stimulation (ES) target locomotor circuits via the activation of sensory afferents. In the uninjured mouse, afferent input to Shox2 INs is either excitatory or inhibitory in near equivalent proportions. After chronic complete SCI, there is an excitatory shift in afferent input to Shox2 INs. Sensory-evoked inhibitory input to Shox2 INs can be restored by sub-motor-threshold ES. This suggests that inhibitory INs involved in sensory afferent pathways to Shox2 INs are a novel point of plasticity, and a potential therapeutic target following SCI. Previous characterization of the inhibitory INs with connections to Shox2 INs demonstrated that they are predominantly glycinergic in neurotransmitter phenotype, rather than GABAergic. Additionally, glycinergic INs with connections to Shox2 INs are largely restricted to the medial deep dorsal horn. In this study, we further characterized medial laminae V/VI glycinergic INs by molecular marker. Transgenic mouse lines and immunohistochemistry were used to evaluate the overlap of medial laminae V/VI glycinergic INs with Parvalbumin, Prox1, RORβ, Tfap2β and Satb2. No single molecular marker labels all of the glycinergic INs in medial lamina V/VI, and all five of the markers label varying proportions of glycinergic INs in this region. This region coincides with an area containing dense parvalbumin labeling, indicating that it is a termination zone of proprioceptive afferent terminals. Ongoing studies will determine whether deep dorsal glycinergic INs with connections to Shox2 INs belong to a molecularly identifiable subset of these neurons and will investigate the sensory afferent input that they receive. These findings identify a molecularly diverse population of glycinergic neurons that are presynaptic to Shox2 INs and potentially involved in the inhibitory control of Shox2 INs by low threshold afferent pathways.

Disclosures: J.R. McGrath: None. **D. Garcia-Ramirez:** None. **K.J. Dougherty:** None.

Poster

PSTR121: Interneurons and Motor Neurons

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council 2017-02905
Wallenberg Foundation KAW 2018.0010
Swedish Brain Foundation FO2021-0317
Karolinska Institutet

Title: Real-time proprioception for locomotor dynamics and collective coordination

Authors: *D. MADRID-PULGARIN[1], L. D. PICTON[1], A. PAZZAGLIA[2], J. ARREGUIT[2], A. FERRARIO[2], C.-X. HUANG[3], P. FONTANEL[1], J. SONG[3], A. J. IJSPEERT[2], A. EL MANIRA[1];

[1]Karolinska Inst., Stockholm, Sweden; [2]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [3]Tongji Univ., Shanghai, China

Abstract: The successful execution of motor actions in an ever-changing world depends upon the ability to detect and integrate environmental cues and sculpt motor outputs accordingly. Motor actions need to be adjusted to compensate for external perturbations, even when they occur rapidly and unexpectedly. In some contexts, such as schooling in fish, the flow fields generated by other animals can even be exploited and allow groups of fish to use sensory feedback to act collectively and save energy. While these motor adjustments may involve complex, high-dimensional top-down computations, it is unclear whether a simplified, low-dimensional proprioceptive circuit with short delays can effectively perform the rapid computations needed for real-time adjustments. We previously identified a population of piezo2+ intraspinal, inhibitory proprioceptors in the adult zebrafish that are activated upon bending of the body. In this study, we show that curvature-based feedback from these specialized proprioceptors not only contributes to locomotor rhythm-generation, but also provides a mechanism for the compensation and synchronization of motor commands in relation to environmental signals. We show that the direct inhibition of rhythm-generating V2a interneurons (INs) from proprioceptors provides an early burst termination cue, narrowing the excitation window in V2a INs, thus leading to an increase in swim frequency. We now also show that these proprioceptors provide direct inhibition to dI6 commissural inhibitory INs. This connection provides a complementary burst initiation cue in contralateral V2a INs during swimming, further contributing to increased swim frequency. This direct control over V2a and dI6 INs also allows for rapid compensatory adjustments of motor output intensity when the body is displaced to one side during locomotion and provides a mechanism for entraining the network frequency upon imposed rhythmic movements. A functional role for this entrainment mechanism was explored by testing the effect of piezo2 channel knockout on schooling behavior. Zebrafish lacking piezo2-dependent proprioceptive feedback showed significant coordination deficits during group dynamics and were ultimately unable to perform schooling behavior. Our results reveal a critical role of piezo2-mediated proprioception in locomotor rhythm-generation; in motor compensation to external forces; and in the ability to collectively coordinate motor behavior. Finally, we recapitulate these findings using a computational model of the sensorimotor circuit for locomotion in adult zebrafish, allowing us to further test hypotheses that are experimentally unfeasible.

Disclosures: D. Madrid-Pulgarin: None. **L.D. Picton:** None. **A. Pazzaglia:** None. **J. Arreguit:** None. **A. Ferrario:** None. **C. Huang:** None. **P. Fontanel:** None. **J. Song:** None. **A.J. Ijspeert:** None. **A. El Manira:** None.

Poster

PSTR121: Interneurons and Motor Neurons

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Program #/Poster #: PSTR121.06/E4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ANR-21-CE17-0060

Title: Sk2 channels coupling to t-type ca^{2+} channels dictate the emergence of bursting activities in the central pattern generator for locomotion in mice.

Authors: F. KRUST, C. BROCARD, ***F. BROCARD**;
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Abstract: The spinal Central Pattern Generator (CPG) governs rhythmic activities in spinal motoneurons essential for locomotion. This rhythm emerges from glutamatergic interneurons, some of which exhibit inherent membrane oscillations known as pacemaker bursting activities. These oscillations rely on the persistent sodium current (I_{NaP}), crucial for generating the locomotor rhythm (Tazerart et al., 2007, 2008). Our studies have shown that changes in levels of extracellular Ca^{2+} ($[Ca^{2+}]_o$) and K^+ ($[K^+]_o$) during locomotion, enhance pacemaker function by amplifying I_{NaP} but also by reducing K^+ currents (Brocard et al., 2013; Verneuil et al., 2020). While our recent work highlighted the cooperative role of *Nav1.1* and *Nav1.6* channels in producing I_{NaP} within the CPG (Drouillas et al., 2023), a gap remains in identifying the K^+ channels or currents involved. The slow Ca^{2+}-activated K^+ current (I_{KCa}) emerges as a prime candidate, noted for its sensitivity to changes in $[Ca^{2+}]_o$ and $[K^+]_o$. In this study, using *in vitro* mouse preparations, we explored which SK channels mediate I_{KCa} and their role in regulating bursting activities of CPG interneurons. Blocking SK channels with apamin resulted in a shift from tonic spiking to I_{NaP}-dependent bursting in approximately half of the patch-clamp recorded cells in the ventromedial regions of the CPG (L1-L2). Conversely, increasing SK channel activity with 1-EBIO abolished bursting activities. Immunohistochemical analyses identified clusters of SK2 channels in both interneurons and motoneurons. Similarly, inhibiting SK2 channels with tamapin, like apamin, unmasked comparable bursting activities in CPG interneurons. Investigating the Ca^{2+} sources activating SK2 channels, we found that blocking T-type Ca^{2+} channels with mibefradil or Nickel replicated the effects seen with apamin and tamapin, whereas blocking L-type or P/Q-type Ca^{2+} channels with nifedipine and conotoxin had no effect. Our findings confirm that Ca^{2+} flow through T-type channels directly influences SK2 channel function, bypassing the need for Ca^{2+}-induced Ca^{2+} release. Overall, this study emphasizes the role of SK2 channels in mediating I_{KCa} and in regulating the emergence of pacemaker bursting cells, while identifying the primary Ca^{2+} sources required for their activation. These insights deepen our understanding of the ion mechanisms driving locomotor rhythmogenesis and provide a solid basis for further *in vivo* studies on the role of SK2 channels within the spinal locomotor network.

Disclosures: F. krust: None. **C. Brocard:** None. **F. Brocard:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.07/E5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant R35 NS097343

Title: Increased robustness and adaptation to simultaneous temperature and elevated extracellular potassium in the pyloric rhythm of the crab, Cancer borealis

Authors: *M. LEE[1], E. E. MARDER[2];
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Abstract: Title: **Increased Robustness and Adaptationto Simultaneous Temperature and ElevatedExtracellular Potassium in the Pyloric Rhythm of the Crab,*Cancerborealis***Authors: Margaret Lee and Eve MarderThe pyloric circuit is a central pattern generator that is responsible for filtering food through theforegut of the crab, *Cancerborealis.*Within the pyloric circuit, temperature and elevatedextracellular potassium have been extensively studied. When perturbed with a 2.5-fold increasein extracellular potassium concentration, the pyloric rhythm initially loses its bursting activity,then quickly adapts to its new environment and resumes close to normal activity. In this study weexamine the effects of two global perturbations, elevated extracellular potassium (highK^+)andhigh temperature on the resilience of the pyloric rhythm. To study the temperature dependence ofthe adaptation, we expose the stomatogastric ganglion (STG)preparation to high K^+ at twotemperatures, 11°C—the stereotypical control temperature—and 20°C. We find that at highertemperatures, the preparations are able to recover to bursting activity more readily and also beginspiking earlier than preparations at 11°C. In conclusion, high temperature increases therobustness of the preparation to perturbation by high potassium saline, suggesting there may beparallel pathways that promote this phenomenon.

Disclosures: M. Lee: None. **E.E. Marder:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.08/E6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JSPS KAKENHI Grant 23H04213

Title: A higher-order interneuron that orchestrates intersegmental coordination in axial locomotion

Authors: *T. SEKI[1], H. KOHSAKA[2,3], A. NOSE[4,5];
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Univ. of Tokyo, Chiba, Japan; [5]Department of Physics, Graduate School of Science, The University of Tokyo, Tokyo, Japan

Abstract: Axial locomotion, in which muscle contractions occur sequentially along the chain of body segments, is a ubiquitous form of locomotion across animal species, and includes walking in vertebrates as well as crawling and swimming in limbless animals. A key element of this type of locomotion is intersegmental coordination. However, how the activity of motor neurons and upstream interneurons are regulated across segments to output intersegmentally coordinated muscle contractions remains incompletely understood. We use the forward crawling of *Drosophila* larvae as a model to address this problem. Larvae achieve forward crawling by propagating muscle contractions sequentially from posterior to anterior body segments. Although several local premotor interneurons involved in the forward movement are identified, how the complex pattern of their activities is controlled in an intersegmentally coordinated manner remains unclear. Here we report a novel interneuron, A18f, that is responsible for intersegmental coordination during forward crawling. A18f is an ascending excitatory neuron that projects to up to several body segments anteriorly. Calcium imaging revealed that A18f is specifically active during the forward but not backward locomotion. In addition, connectomics analysis revealed that A18f provides inputs across multiple body segments to many lower-order premotor interneurons, including the A27h and GDL neuron previously shown to be involved in sequential activation of motor neurons during forward crawling. Consistent with this, optogenetic activation of a single A18f neuron induced muscle contractions in anterior body segments. Furthermore, optogenetic inhibition of A18f neurons strongly inhibited larval forward crawling, suggesting that A18f plays a central role in forward crawling. These results suggest that A18f neurons coordinate the overall motor circuit during forward crawling by simultaneously activating a number of downstream neurons across segments at appropriate timing. This study demonstrates that intersegmental coordination in *Drosophila* larval axial locomotion is orchestrated by higher-order interneurons.

Disclosures: T. Seki: None. **H. Kohsaka:** None. **A. Nose:** None.

Poster

PSTR121: Interneurons and Motor Neurons

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.09/E7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: 3R35 NS097343
5T32 NS007292

Title: $I_h$block reveals separation of timescales in C. borealis pyloric rhythm temperature response

Authors: *K. SCHAPIRO[1], J. RITTENBERG[4], M. KENNGOTT[2], E. MARDER[3];
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Abstract: Motor patterns operate over a range of frequencies and often transition smoothly and monotonically within a particular pattern (e.g. normal vs speed walking). We investigated the contribution of the hyperpolarization-activated inward current (I_h) to the frequency of the pyloric rhythm of the stomatogastric ganglion (STG) of the crab, *Cancer borealis* as temperature was altered from 11°C to 21°C. Under control conditions, changes in the pyloric frequency match the dynamics of a temperature change, such that an increase in temperature results in a concomitant pyloric frequency increase. Blocking I_h with cesium (Cs^+) revealed that I_h plays an important role in determining the dynamics of the temperature-induced frequency change (transient response) and the magnitude of the frequency change (persistent response). Surprisingly in Cs^+ the frequency displayed non-monotonic dynamics during temperature transitions; the frequency initially dropped as temperature increased, then rose once temperature stabilized, creating a characteristic "jag". Interestingly, these jags were still present during temperature transitions in Cs^+ when the pacemaker was isolated by picrotoxin, indicating the transient response is mediated by intrinsic properties of the pacemaker. Cs^+ also affected the magnitude of the persistent frequency response to temperature increases, such that the increase in pyloric frequency with temperature diminished and the Q_{10} of the pyloric frequency dropped from ~1.75 to ~1.35. Unlike the effect of Cs^+ on the transient response, the magnitude effect was mediated by network feedback, as when the pacemaker was isolated from feedback with picrotoxin, there was no longer a significant effect of Cs^+ on the steady state frequency increase. Overall, these data suggest that I_h plays an important role in the ability of this circuit to produce smooth transitory responses and persistent frequency increases by different mechanisms during temperature fluctuations.

Disclosures: K. Schapiro: None. **J. Rittenberg:** None. **M. Kenngott:** None. **E. Marder:** None.

Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.10/E8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH U19 NS107466
NSF 2239412

Title: Transcriptomic and spatial homology of cell types in the medulla and spinal cord

Authors: *J. P. VINCENT, M. MOYA, M. ECONOMO;
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Abstract: The medulla and spinal cord are contiguous structures of the caudal central nervous system that share many anatomical and functional features. Both contain the cell bodies of motor and sensory neurons and interneurons and contain genetically pre-programmed circuits essential for nearly all aspects of sensation and action. Transcriptomic analysis of the medulla and spinal cord has revealed the existence of hundreds of unique cell types in each area. Yet it remains unclear to what degree these types are conserved between the two structures, both at the molecular level and in terms of their spatial arrangement. Here, we integrate single-cell RNA sequencing and spatial transcriptomic data collected in the medulla and spinal cord to determine (1) the degree of homology that exists across cell types in both structures, and (2) whether homologous cell types show conserved spatial organizations. We find that many motor and sensory types in dorsal and ventral laminae of the spinal cord are directly conserved in the medulla, while fewer homologous types can be found for neurons in more intermediate laminae. Sensory, inter-, and motor neurons canonically arrange themselves on a dorsoventral gradient in the spinal cord, while we find that in the medulla, this sensory to motor gradient is oriented lateromedially. Homology with the spinal cord is most apparent in the caudal medulla, especially in the caudal part of the spinal nucleus of the trigeminal nerve, where transcriptomically conserved sensory types are arranged in a laminar distribution similar to that found in the dorsal horn of the spinal cord. Finally, we show that this homology is most apparent in regions of the medulla expressing Hoxb5, a homeobox gene whose medullary transcription is restricted to developmental rhombomeres 10 and 11.

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Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.11/E9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR MOP 86470
Stollery Children's Hospital Foundation/Women and Children's Health Research Institute

Title: Functional identification and molecular characterization of the neurons involved in mammalian locomotor rhythmogenesis

Authors: V. RANCIC[1], U. HAQUE[2], A. RUANGKITTISAKUL[3], T. YOKOTA[2], ***S. GOSGNACH**[4];
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Abstract: Central Pattern Generators (CPGs) are networks of neurons that are able to produce rhythmic, motor outputs in the absence of sensory or descending input. Work in my laboratory

focuses on the mammalian locomotor CPG which is primarily situated in the intermediate laminae of the caudal spinal cord, and is responsible for the basic rhythmic activity that is characteristic of stepping in all mammals studied, including humans. While a genetic approach has been used to identify the specific function of several populations of neurons that make up this network, a population of cells that is both necessary and sufficient for generating the locomotor rhythm in the spinal cord has yet to be deciphered. Recently my laboratory has developed an experimental approach that enables calcium activity in neurons across the transverse plane of the spinal cord to be visualized during locomotor activity. This approach facilitates the visual-identification of rhythm generating neurons based on their ability to burst rhythmically during locomotion, and also exhibit intrinsic oscillation while synaptically isolated- an essential feature of rhythmogenic neurons. Analysis of 98 putative rhythm generating neurons indicates that they are primarily situated within a 200µm radius of the central canal and project axons ipsilaterally, towards ventrolateral targets. Finally, single cell patch-seq analysis was incorporated to identify the genetic makeup of these neurons and determine whether a molecular signature can be identified. Our results provide key information regarding the organization of mammalian locomotor circuits. Furthermore, the identification of a molecular signature for rhythmogenic neurons provides clearly-defined targets for those attempting to restore motor control after spinal cord injury.

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Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.12/E10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH/NINDS R01NS109552
CIHR PJT 165823
NIH R01 NS047567

Title: Standing up and maintaining posture during locomotion is coordinated by V3 neurons

Authors: V. RANCIC[1], H. ZHANG[2], A. M. LUCAS-OSMA[3], A. MAHROUS[4], M. K. CHARDON[4], R. LETAWSKY[5], K. HARI[6], M. ALMOKDAD[3], C. HECKMAN[7], Y. ZHANG[8], *D. BENNETT[3], K. K. FENRICH[2];
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Abstract: Many of the neurons that control rhythmic movements like walking reside in the spinal cord in the central pattern generator (CPG), and thus understanding this CPG has been a major focus of rehabilitation efforts after spinal cord injury (SCI). However, the prerequisites for walking are steady postural tone and ability to stand, which are permanently lost following severe SCI. While little is known about the spinal circuits that control posture to some extent postural tone spontaneously recovers after SCI, but it is poorly controlled, in the form of tonic muscle spasms. In the course of our recent studies of tail muscle spasms in mice, we unexpectedly found that sacral propriospinal commissural neurons (V3 neurons; Sim1+; glutamatergic) play an essential role in generating postural-like muscle spasms after SCI, with optogenetic activation or inactivation of these neurons triggering or blocking spasms. Thus, we investigated here whether more generally lumbar V3 neurons function as key postural control neurons for standing and trunk stability. Our results indicate that brief bilateral optogenetic activation of upper lumbar V3 neurons induces coordinated standing in awake intact and injured mice (Sim1//ChR2 mice). After SCI this V3 neuron activation can overcome hindlimb paralysis, whereas silencing these neurons impairs weight support. V3 activation of standing occurs independently of walking: it can both terminate ongoing walking in favor of standing, or initiate a sit-to-stand posture that precipitates walking in both intact and injured mice. V3 neurons regulate standing by possessing intrinsic persistent sodium currents that generate sustained activity, and by broadly innervating motoneurons over the entire lumbosacral spinal cord. Remarkably, we find that most V3 neurons fire tonically during locomotion, and thus bypass the CPG actions, suggesting that many V3 neurons receive little rhythmic drive from the CPG. That is, by using calcium imaging of V3 neuron input to motoneurons during brainstem induced locomotion (in ex vivo neonatal Sim1//GCaMP8s mice) we observe that the majority of V3 neurons exhibit tonic activity, with relatively little phasic activity synchronized with the locomotor output (< 20% modulation depth, especially in medial and ventral V3 neurons). Furthermore, in vivo recordings from putative V3 neurons (laminae VIII propriospinal commissural neurons) confirms tonic firing associated with postural muscle tone. Together these findings demonstrate that V3 neurons form a novel spinal circuit that independently generates posture, and targeting these neurons provides the necessary weight support to restore walking after SCI.

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Poster

PSTR121: Interneurons and Motor Neurons

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR121.13/E11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant T32MH067564-21
The Picower Institute for Learning and Memory
The JPB Foundation

Title: Computational Modeling of Clytia Hemisphaerica Swim Motor Neurons

Authors: *R. LU[1], K. CUNNINGHAM[2], B. WEISSBOURD[2], A. KENNEDY[1];
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Abstract: *Clytia hemisphaerica*, a hydrozoan jellyfish, has recently emerged as a model organism for systems neuroscience. *Clytia*'s neurons are homologous to those of mammals, but it lacks a central nervous system and instead has two nerve rings and a diffuse nerve net. Nevertheless, these structures have complex functional organization and can produce behaviors and internal states. During swimming, the inner nerve rhythmically activates circularly oriented striated muscles. Interestingly, *Clytia* exhibits remarkable decentralization of control of this rhythm; excision experiments have demonstrated that small and arbitrarily located regions of the ring can produce periodic swim contractions. Previous electrophysiology work in a closely related jellyfish species also reveals resting membrane potential oscillations with bursts of firing before contractions. The mechanism for this pulse generation is unknown. Additionally, how this activity is modulated to stop swimming or to contract asymmetrically as in turning is unclear. Using Rinzel and Lee's models of the parabolic bursting Aplysia R-15 neuron as a starting point, we developed a single-cell Hodgkin-Huxley-like computational model for intrinsic oscillatory behavior in *Clytia* inner nerve ring neurons. We found parameter regimes that increased the oscillation frequency from 0.1 Hz in the original model to approximately 4 Hz, to match the *Clytia* swim rhythm. Bifurcation analysis shows that despite a similarity in time scales, the spiking mechanism of the model can be dissociated from the subthreshold mechanism, allowing for future reduction of the model. We next explored two alternative models by which oscillations in calcium concentration might drive periodic spiking. In one model, activation of a calcium-gated potassium channel is necessary to decrease the calcium concentration at the peak of its oscillation, and in the other, the inactivation of a calcium-gated calcium channel is required. Interestingly, a decrease in the potassium reversal potential increases the oscillation frequency in the potassium-activation model but decreases the frequency in the calcium-inactivation model, suggesting that experimental modification of extracellular potassium concentrations can reveal which model is more probable. Going forward, our models pave the way for further study of *Clytia*, for example by coupling together a ring of single-cell model neurons to understand how a network of oscillating cells can be modulated to produce different behaviors.

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Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.01/E12

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Exploring The World Together: Differences in Individual and Joint Open Field Exploration

Authors: *N. E. CAMPBELL[1], A. AMIDEI[1], D. KOVALEV[2], S. CIOSEK[2], O. AKINBO[1], A. J. GRIPPO[1];
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Abstract: Social bonds are critical for maintaining optimal health conditions, especially as individuals age. Social isolation and partner loss have lasting acute and chronic effects on the stress response. Prairie voles have been validated as an animal model to study monogamous social bonding and interactions of stress, depression, and anxiety within social bonds. Little research has explored how the presence of a long-term social partner can affect exploration and anxiety-related behaviors within an open field in aging prairie voles. Therefore, the current study investigated the effect of long-term pair bonding on behavioral and physiological correlates of exploratory behavior. 35 long-term pair-bonded aged (~20 months) male and female prairie voles were used in this study. Voles explored the open field either with their bonded partner or alone for a total of 20 minutes. The locomotion was analyzed for measures of duration in center/perimeter, duration of grooming and rearing behaviors and escape attempts. Additional measures were observed in the pair-bonded exploration condition, including joint exploration, aggressive behaviors and positive social behaviors. Blood plasma was collected after the open field and analyzed for circulating corticosterone levels. Results indicated that the voles who explored the open field with their partner displayed significantly lower levels of circulating corticosterone and spent significantly more time in the center of the open field, as compared to voles that explored the open field alone. These patterns suggest that joint open field exploration may have anxiolytic effects and physiological stress-reducing effects. Understanding the behavioral and hormonal effects of joint open exploration provide insight as to how the presence of a bonded partner may be anxiolytic, ultimately changing behavior within an anxiety-inducing environment. This study is foundational for future studies that could investigate how losing a partner can affect additional behaviors within the open field as well as behavioral, physiological, and neural responses to other acute stressors.

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Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.02/E13

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant AG064091
NIH Grant P51OD011133

Title: Does Social Support Buffer Responses to Separation from a Long-Term Partner?

Authors: *K. A. PHILLIPS[1], M. LOPEZ[2], M. BOISSELIER[3], C. ROSS[4], J. P. CAPITANIO[5]; [1]Neurosci. Program, [2]Psychology, [3]Neurosci., Trinity Univ., San Antonio, TX; [4]Texas Biomed. Res. Inst., San Antonio, TX; [5]California Natl. Primate Res. Ctr., Univ. of California Davis, Davis, CA

Abstract: The loss of a long-term partner frequently leads to loneliness, contributing to cognitive dysfunction in part by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Marmosets (*Callithrix jacchus*) provide a unique biomedical model to examine the impact of social isolation and social buffering on cognition and neuroendocrine function as they form long-term socially monogamous partnerships. We tested the effects of social buffering on cognition in aged marmoset pairs, when separated for 3-months and placed with a novel companion or remaining alone. HPA-axis function was evaluated at the end of the 3-month period. Original pairs were then reunited, followed by HPA-axis evaluation 1-month later. We expected those separated and alone would display acute shifts in cognition and dysregulation of the HPA axis compared to individuals separated but paired with a novel partner. As expected, cognitive performance declined for animals in the alone condition ($p<0.05$). Males has higher cortisol than females in the alone condition ($p<0.05$), and lower cortisol than females in the novel condition ($p<0.05$). The effects of condition during the 3-month separation period persisted into the reunion period; presence of a novel partner did not buffer the physiological stress response. These results suggest reunion with the partner had different effects based on whether one had been alone or with a novel partner, and this effect was moderated by sex.

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Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.03/E14

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: UNAM-DGAPA-PAPIIT IN204824
INPER 2022-1-13
CF-2023-G-206 CONAHCYT

Title: Relevance of environmental enrichment on anxiety and depression-like behaviors in female praire voles following pair bond disruption

Authors: *A. LUIS CASTAÑEDA[1], A. E. CASTRO[2], F. CAMACHO[1], R. G. PAREDES[3], N. F. DIAZ[4], W. PORTILLO[5];
[1]Inst. de Neurobiología, UNAM, Querétaro, Mexico; [2]Inst. De Neurobiología-UNAM, Queretaro, Mexico; [3]ENES/INB UNAM, Querétaro, QRO, Mexico; [4]Inst. Nacional de Perinatologia, Mexico City, Mexico; [5]Inst. DE NEUROBIOLOGIA, QUERETARO, Mexico

Abstract: Prairie voles are socially monogamous rodents known for establishing long-term pair bonds. Previous studies have demonstrated that partner isolation induces depressive and anxiety-like behaviors, akin to grief in humans. Conversely, environmental enrichment (EE) has been shown to effectively reduce affective disturbances observed after social isolation in both male and female voles. Our aim was to implement an enrichment protocol to assess the impact of EE on anxious and depressive-like behaviors in female voles following pair bond disruption due to isolation.Pair bonds were induced in female voles through five-day cohabitation with males. Subsequently, they were randomly allocated to one of the following groups: a) social cohabitation with mating (SCM; n=5), females that remained with their sexual partner for the following fifteen days; b) bond disruption due to isolation (BD; n=5), females whose pair bond was disrupted due to removal of the sexual partner followed by fifteen days of isolation and c) bond disruption due to isolation followed by EE (BD+EE; n=4), females that were separated from their mates; first, five days in standard conditions and later, ten days in EE. EE comprised an enlarged housing area containing different colored plastic tunnels and novel items designed for cognitive, sensory, and physical stimulation. The open field test, elevated plus maze, and forced swim test were performed to evaluate anxiety and depression-like behaviors. Our preliminary findings suggest that pair bond disruption due to isolation increases anxiety and depression-like behaviors, even among voles subjected to EE. Further studies are required to delineate the optimal EE conditions in prairie voles capable of attenuating the anxiolytic/depressive effect of bond disruption.

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Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

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Program #/Poster #: PSTR122.04/E15

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: FPIS2024-INPER-7680
INPER 2022-1-13
UNAM-DGAPA IN204824
CONACHYT CF-2023-G-206

Title: Neurobiological insights into pair bond formation: transcriptomic analysis in Microtus ochrogaster

Authors: *D. AVILA-GONZÁLEZ[1], I. ROMERO MORALES[1], M. GARCÍA PÉREZ[1], R. G. PAREDES[2], N. F. DIAZ[1], W. PORTILLO[3];
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Abstract: Pair bonding (PB) refers to the enduring association between two sexually mature adults, with implications for the mental and physiological health of individuals. The dynamics of PB in humans are highly complex because of the social and cultural components, rendering the study of this behavior challenging. The prairie vole (*Microtus ochrogaster*) is one of the few socially monogamous mammals that have been used to elucidate the neurobiological basis of this phenomenon. Previously, we reported that social interaction and mating increased cell proliferation and differentiation into neurogenic niches in both male and female voles, suggesting that neurogenesis is a plastic mechanism involved in the formation and establishment of PB. As a first approach to elucidate the molecular machinery involved in regulating neurogenesis during PB formation, we conducted bulk RNA-seq analysis to identify differentially expressed genes (DEGs) in the SVZ and DG. Functional enrichment analysis was performed using G:Profiler. We established the following sociosexual groups: females (Fe) and males (Ma) in social cohabitation with mating (SCM) for 48 h (48FeSCM, 48MaSCM) or 120 h (120FeSCM, 120MaSCM), as well as control (Co) individuals without cohabitation and isolated individually during the same period as PB formation (48FeCo, 48MaCo, 120FeCo, 120MaCo). Additionally, we compared the gene expression profiles in the SVZ and DG as follows: 1) between sociosexual groups (Co vs. SCM) for each sex and period, and 2) between time periods (48 vs. 120) for each sex and sociosexual group. Interestingly, we observed differential expression of genes involved in epigenetic mechanisms. In the male SVZ, L3mbtl (L3mbtl Histone Methyl-Lysine Binding Protein 1) and Zcwpw1 were downregulated in 48MaSCM compared with 48MaCo. L3mbtl contributes to transcriptional repression by binding histones in a methylation status-dependent manner, whereas Zcwpw1 is a histone methylation reader specific for H3K4me3 and H3K36me3 marks. Additionally, Auts2 was downregulated in the 120h when group compared to 48h group in both sexes. In female voles, 120FeCo showed downregulation of genes with respect to 48FeCo in the DG, whereas in the male SVZ, the expression of Auts2 decreased in 120MaCo and 120MaSCM as compared with 48MaCo and 48MaSCM, respectively. This gene encodes a protein that forms a complex with PRC1, and plays a role in transcriptional activation in the brain. The functional validation of these epigenetic mechanism-associated genes in regulating neurogenesis for the establishment of sociosexual behavior in prairie voles remains to be determined.

Disclosures: D. Avila-González: None. **I. Romero Morales:** None. **M. García Pérez:** None. **R.G. Paredes:** None. **N.F. Diaz:** None. **W. Portillo:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.05/E16

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIMH Grant R01 MH125411

Title: The role of the kappa opioid system in social buffering among pair-bonded titi monkeys

Authors: *J. PAULUS[1], C. MANCA[2], A. D ALMEIDA[2], A. CACERES[3], M. SOSNOWSKI[4], B. HOBSON[2], A. CHAUDHARI[2], K. L. BALES[5];
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Abstract: Strong social connections have been found to protect against mental and physical health issues in humans. One potential explanation for this protective effect is that social partners can help buffer against stressors. We hypothesized that social partners reduce stress-induced release of dynorphin, a peptide associated with negative affect and feelings of dysphoria. Using PET imaging, we investigated the involvement of kappa opioid receptors (KORs) and dynorphin release in social buffering in response to a physical stressor (blood draw) in pair-bonded coppery titi monkeys (n=20), a unique non-human primate model of pair bonds. We employed [11C]GR103545 PET scans to assess kappa opioid receptor binding potential under three social conditions: baseline (no stressor, with mate), stress (blood draw without mate for 30 minutes), and social buffering (blood draw with mate for 30 minutes). Following the 30-minute period, subjects were anesthetized in preparation for the PET scan and a second blood draw was performed to measure changes in plasma cortisol levels. Our results revealed sex differences in the social buffering condition across various brain regions. Males showed significantly higher [11C]GR103545 binding in the amygdala ($p = 0.003$) and hippocampus ($p = 0.008$) during social buffering compared to females, suggesting reduced dynorphin release in males when a partner is present. The amygdala also displayed significantly higher radioligand binding in the stress condition than in the buffering condition ($p = 0.001$), indicating that the presence of a partner reduced KOR activity. Additionally, we found a significant effect of social condition on plasma cortisol levels ($p < 0.001$), with cortisol levels in the stress condition being significantly higher than both the buffering ($p = 0.034$) and baseline ($p < 0.001$) conditions. These findings highlight the role of the kappa opioid system in stress buffering within pair-bonding primate species and contribute to our understanding of the neurobiological mechanisms underlying social buffering and social separation in pair-bonded animals.

Disclosures: J. Paulus: None. **C. Manca:** None. **A. D Almeida:** None. **A. Caceres:** None. **M. Sosnowski:** None. **B. Hobson:** None. **A. Chaudhari:** None. **K.L. Bales:** None.

Poster

PSTR122: Pair Bonding and Sociability

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.06/E17

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: UCD Graduate Student Research Award

Title: Exploring the seahorse brain: differential gene expression and neuroanatomical mapping

Authors: *S. L. MEDEROS[1], A. M. H. SEELKE[2], K. L. BALES[3];
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Abstract: Pair bonding involves complex social behavior often linked to evolutionary advantages such as increased reproductive success and offspring survival. While extensively studied in mammals and birds, the neural mechanisms underlying pair-bonding behaviors in non-traditional species, such as the lined seahorse (Hippocampus erectus), remain largely unexplored. Seahorses, with their unique reproductive biology where males carry and birth offspring, present an intriguing model to investigate the neurobiological basis of pair bonding and monogamy. In this study, we employ Fluorescent In Situ Hybridization (FISH) techniques to elucidate sex-specific and spatially explicit gene expression patterns associated with pair bond formation in seahorses, comparing individuals with and without pairing experience. We will measure gene expression related to cell types (Rbfox3-neurons, Sox9b-astrocytes, Sall1a-microglia), social behavior (Avpr1a- vasopressin receptor, Oxtr-oxytocin/isotocin receptor, Neural cilia-Tmem107, Rsph1), and functionality (tpr1a-Calcium ion channel, Mapk1-map kinase). By shedding light on the neurobiological underpinnings of pair bonding in seahorses, this research will contribute to a deeper understanding of social behaviors across diverse animal taxa and shed light on the evolutionary origins of complex social systems. Furthermore, insights gained from studying seahorse reproduction may have implications for conservation efforts and the management of breeding facilities, where understanding reproductive strategies and social dynamics has been a limiting factor for their success.

Disclosures: S.L. Mederos: None. **A.M.H. Seelke:** None. **K.L. Bales:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

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Program #/Poster #: PSTR122.07/E18

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIGMS NRSA Postdoctoral Fellowship F32GM153130
NIGMS Grant R35GM142799
Beckman Young Investigator Award
University of Houston National Research University Fund Startup R0503962

Title: Neuroendocrine control of subordinate social status by androgen receptors in an African cichlid fish

Authors: *K. M. MUNLEY[1,2], S. RANKOTHGEDERA[1], A. A. HOANG[1], P. H. GUNARATNE[1], B. A. ALWARD[1,2];
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Abstract: Androgens are essential in regulating physiological mechanisms and behaviors associated with social rank. Prior research from our lab has shown that the two androgen receptors present in teleost fishes, ARα and ARβ, control distinct aspects of dominant social status in male *Astatotilpia burtoni*, a highly social African cichlid fish. ARα is necessary for the expression of dominant-typical behaviors (e.g., aggression, mating), whereas ARβ is necessary for the expression of dominant-typical physiological characteristics (e.g., testes growth, bright coloration). It is unclear, however, how androgenic signaling modulates subordinate social status. Here, we characterized the neuroendocrine control of social subordination by androgen receptors in male *A. burtoni*. Specifically, we used ARα and ARβ knockout fish to disentangle the functions of these receptors in regulating physiological and behavioral traits of subordinate social status, including gonadosomatic index (GSI) and submissive behaviors (e.g., fleeing, grazing, freezing). We determined that subordinate ARα and ARβ mutants show different deficits in reproductive physiology: ARα mutants have a *higher* GSI, while ARβ mutants have a *lower* GSI than wild-type fish. Moreover, our preliminary data suggest that ARα and ARβ have distinct roles in controlling subordinate-typical behaviors: ARα mutants display *more* fleeing, grazing, and freezing, whereas ARβ mutants show *less* fleeing, grazing, and freezing relative to wild-type fish. In ongoing work, we are identifying cell type-specific gene programs in the hypothalamus of subordinate males that are perturbed by AR genetic deletion via single-nucleus RNA sequencing. Collectively, these findings will enhance our understanding of the precise neural and molecular mechanisms that govern subordination in group-living species.

Disclosures: K.M. Munley: None. **S. Rankothgedera:** None. **A.A. Hoang:** None. **P.H. Gunaratne:** None. **B.A. Alward:** None.

Poster

PSTR122: Pair Bonding and Sociability

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.08/E19

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: GSE246731
OD P51OD011132
NIH R01 GM144560

Title: Cellularly Resolved Transcriptomic and Epigenomic Transformation of the Preoptic Area During Protandrous Sex Change

Authors: *G. GRAHAM[1], E. IBANEZ[2], C. G. PARKER[3], M. G. CONNOLLY[4], K. N. LEATHERBURY[5], Z. V. JOHNSON[6], T. STREELMAN[7], J. S. RHODES[8];
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Abstract: All false clown anemonefish *Amphiprion ocellaris* begin life as males and undergo protandrous (male-to-female) sex change if they sense they are at the top of their social dominance hierarchy. Thus, in these fish, sex is a plastic trait regulated by the brain rather than genetics. During sex change, the brain orchestrates and maintains a complete restructuring of behavior, endocrinological profile, and gonadal composition. To enable such a transformation, extensive reorganization of the forebrain is necessary. Recently we documented widespread sex differences in the numbers and transcriptomes of several types of neurons and glia in the preoptic area (POA) and dorsal telencephalon using single nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics. However, the temporal order of when these neurobiological changes arise relative to the endocrinological and gonadal changes remains unknown. Therefore, we performed a single nucleus-multiome analysis of the POAs of 10 fish that were 6 months into the process of sex change (along with 6 differentiated male and female controls). One of the sex-changing fish had completed sex change by the end of the 6-months as indicated by fully developed oocytes in the gonads, a female sex steroid hormone profile, and a female behavioral profile. Two of the sex-changing fish were late in the process of sex change as indicated by zero testicular tissue and an expanded gonad with non-vitellogenic oocytes, and a female behavioral profile. The remainder had various amounts of testicular tissue left, along with higher male sex steroid levels, and a heightened male behavioral profile. The POA multiome data are currently being processed. Based on preliminary data, we expect the brains of sex-changing fish with testicular tissue will show increased aromatase gene expression in radial glia, and that these changes will be correlated with increased proportions of neurons expressing cholecystokinin (CCK) and CCK receptors preceding gonadal sex change. In the fish with no testicular tissue and female hormone profile, we expect the brains will look similar to fully differentiated females. The specific sex differences that occur before gonadal and endocrinological feminization are of particular interest because they represent candidates that might be responsible for orchestrating gonadal sex change rather than being induced by female gonadal hormones after gonadal sex change has occurred. This is the first single-cell resolution analysis of the epigenomic and transcriptomic changes that occur in the forebrain of a sex-changing fish during the extraordinary transformation from male to female.

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Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.09/E20

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Early life ultrasonic vocalization production can predict future sociability in C57 mice

Authors: E. CAULEY[1], M. LEMLER[1], N. COFSKY[1], J. WATERS[1], *M. BINDER[2];
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Abstract: Ultrasonic vocalizations (USVs) are a form of communicative behavior that is commonly examined in murine models. USVs are unique in that they precede nearly all other behavioral assessments. However, despite the early occurrence of vocalizations, their relationship to future behaviors are unknown. In the present study, we used C57 mice and assessed USVs on postnatal days 4, 8, and 12. We next calculated the average USV rate throughout development and split the data into a high and a low vocalizer group. We then assessed each mouse's anxiety, sociability, and exploratory behaviors in adults using the social interaction, 3 chamber, and open field tests. We first found that the high vocalizer group produced significantly more USVs than the low vocalizer group. When assessing anxiety and exploratory behavior, we did not find any significant differences between groups nor any significant correlations within groups. However, when assessing social interaction, we found that the high vocalizer group was significantly more social than the low vocalizer group. Furthermore, we found a significant medium correlation between USV production and sociability. To better examine this effect, we compared the two tails of the distribution, where the difference in USV production was most pronounced, and found a significantly larger correlation. To verify that the low vocalizer group did not have an atypical phenotype, we analyzed sociability in the 3 chamber test and observed the expected social preference in both groups. Overall, our data suggests that increased vocalization production in C57 neonates can predict adult sociability.

Disclosures: E. Cauley: None. **M. Lemler:** None. **N. Cofsky:** None. **J. Waters:** None. **M. Binder:** None.

Poster

PSTR122: Pair Bonding and Sociability

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.10/E21

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: K01 MH119540
(Hawk-IDDRC; NICHD; P50 HD103556; PI Abel and Strathearn

Title: Sex differences in basolateral amygdala activity during social approach and interaction

Authors: *D. PREUSCHL[1], S. A. HEINEY[2], E. HAGAN[1], C. TESAR[1], P. QUINONES[3], S. L. FERRI[4];
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Abstract: Nearly all animals exhibit species-specific social behaviors and impairments can decrease well-being, quality of life, likelihood of reproduction and survival. Most neurodevelopmental and neuropsychiatric disorders cause disruptions in sociability, for which there are no targeted treatments. Many brain areas and cell types contribute to social behavior, but underlying mechanisms are still not fully defined. Determining neural signatures during different types of social behaviors and whether they demonstrate sex differences may help elucidate pathophysiology and novel treatment targets of social impairments present in disorders such as schizophrenia and Autism Spectrum Disorder. Here, we are using a genetically encoded calcium indicator and fiber photometry to record activity in the basolateral amygdala (BLA) of male and female wild-type mice during affiliative social interactions. Preliminary data has indicated sex differences in neural activity during social approach as well as social microbehaviors during free interactions; male BLA activity was significantly increased during social sniffing but not investigation of a novel object, rearing, or grooming, and female social behavior was modulated by estrous phase. Both males and females exhibited increased inappropriate reciprocal interactions during chemogenetic inhibition of the amygdalostriatal region. Future experiments will determine how these sex-specific patterns of neural activity during social behavior are altered in mice with social deficits.

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Poster

PSTR122: Pair Bonding and Sociability

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Program #/Poster #: PSTR122.11/E22

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: KAKENHI Grant-in-Aid for Early-Career Scientists JP21K15728

Title: Rfid-based automated home-cage behavioral tracking for group-housed rodents and primates

Authors: *S. BENNER[1], S. SHIONO[2], H.-P. LIPP[3], H. YAMASUE[4], T. ENDO[2];
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Abstract: Behavioral evaluation of laboratory animals is crucial in neuroscience and psychiatry. Automated home cage monitoring (AHCM) is gaining recognition as a viable alternative to

traditional methods, yet error-free identification of group-housed animals remains challenging. Radiofrequency identification (RFID) enables accurate identification of an unlimited number of animals, but existing RFID-based AHCM systems face limitations. Firstly, processing speed decreases as the number of antennas and tags increases, sacrificing spatial resolution for temporal resolution. Secondly, they fail to read multiple animals simultaneously within the antenna's range. To address these limitations, we developed HF (High-Frequency) RFID-based systems, instead of commonly used LF(Low-Frequency), for AHCM applications. We developed two variations of systems compliant with ISO/IEC standards that operate at a speed of 3.55 Hz (locates the tags at least 3 times per sec) and have anti-collision capability. We evaluated our system's precision and reading ranges and demonstrated their applications using group-housed rodents, primates, and aquatic animals. Commercial HF tags (2.12 x 12 mm) were implanted subcutaneously under anesthesia for animal experiments. The first system is a board comprised of multiple 50mm × 50mm-sized antennas arranged side-by-side for placement under the cages. Antennas activate sequentially to read the tag atop them, recording the 2D positional data of the animals continuously. We show an example of tracking 24 mice on a board of 96-antenna. The second system is a series of ring and flat antennas of various sizes to be placed flexibly and three-dimensionally within the experimental environment, at any number, and in any combination. This permits more diverse arrangements that can adapt to more ecological settings and accommodate a variety of animal species. We used this system to track 10 common marmosets in a 44.65 m3 room with enrichment structures. We further tested if our systems can be applied to the aquatic environments, using the Japanese fire-bellied newts and Nile tilapia, and confirmed they are compatible with monitoring animals in the water. Our systems successfully collected log access information for each animal at specific locations to predict their activities (e.g., feeding), and identify movement patterns. Besides basal activity and preference data, we obtained indices of social behavior from temporal-spatial interactions between different animals in socially housed environments. We believe that the methodology presented here can facilitate animal studies in a wide range of neuroscience applications.

Disclosures: S. Benner: None. **S. Shiono:** A. Employment/Salary (full or part-time):; Phenovance LLC. **H. Lipp:** None. **H. Yamasue:** None. **T. Endo:** A. Employment/Salary (full or part-time):; Phenovance LLC.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.12/E23

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Variation in neuropeptide receptor density across dispersal and by sex in Belding’s ground squirrels

Authors: *N. LEE[1], K. POWER[2], S. NUNES[3], A. BEERY[2];
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Abstract: For solitary rodents, dispersal marks a major geographic and social transition away from the close social environment of the natal group. This transition from social to solitary may be promoted by reduced social tolerance for family members, and/or by unrelated factors such as increased exploration and activity. Dispersal has impacts across multiple levels of biological organization, from population genetic diversity to individual fitness. Despite the prevalence and importance of dispersal in many species, the neural mechanisms underlying the timing and initiation of this process remain poorly understood. We conducted an integrative, field-based study of changes in oxytocin receptor (OTR) and vasopressin receptor (V1aR) densities across dispersal in wild Belding's ground squirrels (*Urocitellus beldingi*) in the Eastern Sierras. This population of Belding's ground squirrels have been extensively studied at this field site for decades, providing life-history data for each squirrel and making them an ideal choice for these analyses. While female Belding's ground squirrels typically remain at or near their natal nest through their first season, males disperse away from their family group—transitioning from group living as juveniles to relatively solitary as adults. We collected brains from two age groups of pre-dispersal males and females, as well as from post-dispersal (immigrant) males. OTR density in the central nucleus of the amygdala declined with age and across dispersal in male ground squirrels, with potential implications for developmental shifts in behavior relevant to dispersal. Sex differences in OTR binding were present in the bed nucleus of the stria terminalis. We will also present results of the V1aR assay (currently being analyzed), and relate these results to findings in other species.

Disclosures: N. Lee: None. **K. Power:** None. **S. Nunes:** None. **A. Beery:** None.

Poster

PSTR122: Pair Bonding and Sociability

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Program #/Poster #: PSTR122.13/E24

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH T34GM131939
NIMH-R01 MH121603

Title: Amplifying vasopressin in a sexually differentiated circuit leads to alteration in social and emotional behavior.

Authors: *S. GREGORY[1], C. FRIESEN[1], G. J. DE VRIES[2], A. PETRULIS[1];
[1]Georgia State Univ. Neurosci. Inst., Atlanta, GA; [2]Dept. of Biol., Georgia State Univ., Atlanta, GA

Abstract: The neuropeptide arginine-vasopressin (AVP) system has long been implicated in the regulation of social behavior and communication. AVP-producing cells within the bed nucleus of the stria terminalis (BNST), which represent one of the largest sex differences (male-biased) in vertebrate brains, affect social behavior differently in males and females. Indeed, removing or suppressing the activity of these cells, as well as knocking down AVP production in this cell population, all reduce social approach and investigation in male, but not female, mice. Consequently, we hypothesized that the BNST AVP cell population normally drives male-typical social interest. If so, then artificially boosting AVP in the BNST of females should increase their levels of social interaction in a male-typical way. To test this, we take advantage of the fact that AVP is colocalized with the neuropeptide galanin (GAL) in the BNST to target BNST GAL cells for viral-mediated, cre-dependent overexpression of AVP (or control GFP virus) in GAL-cre+ male and female mice. Preliminary data indicate that boosting AVP expression within the BNST of males increased their investigation of other males, supporting our hypothesis that this system drives male-male investigation. In addition, chronic amplification of AVP in BNST of females increased their anxiety-like behavior, and decreased their investigation of other females. This research contributes to our understanding of how sexually differentiated brain systems, such as AVP, are organized and function and may ultimately lead to better therapeutic interventions for psychiatric disorders characterized by social deficits that are sex different in their prevalence and severity.

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Poster

PSTR122: Pair Bonding and Sociability

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Topic: F.02. Neuroendrocrine Processes and Behavior

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UNAM-DGAPA-PAPIIT IN204718
UNAM-DGAPA-PAPIIT IN205423
CONAHCYT A1S8948

Title: Prolactin effect on reproductive behaviors and electrical activity in the accessory olfactory bulb in adult female mice

Authors: B. ORDAZ[1], V. VIÑUELA-BERNI[1], F. PENA[2], T. MORALES[3], *R. CORONA[4,5]; [1]Inst. de Neurobiología, UNAM, Querétaro, Mexico; [2]Inst. de Neurobiología, UNAM, CDMX, Mexico; [3]Inst. de Neurobiología UNAM, Inst. de Neurobiología, UNAM, Queretaro, Mexico; [4]Natl. Autonomus Univ. of Mexico, Querétaro, Mexico; [5]Instituto de Neurobiología, UNAM, Querétaro, Mexico

Abstract: Prolactin (PRL) participates in reproduction and in the maturation and plasticity of the olfactory bulb (OB). PRL receptors are located within the OB and their absence disrupts some reproductive behaviors. We have shown that high levels of PRL during a juvenile period or an acute administration alters the activation of the accessory OB (AOB) of the female mice, nonetheless the direct effect of PRL in the OB is still unknown. PRL variation levels can alter ovulation periods; however, evidence is missing about consequences on reproductive behaviors. In the current project, we evaluated the effects of PRL in reproductive behaviors. Additionally, we tested the AOB physiological responses by PRL. Naive adult CD1 female mice that were cycling normally received a PRL 10 day-treatment (5mg/kg) to promote hyperprolactinemia. After PRL, females were subjected to olfactory preference and sexual behavioral tests. Finally, we obtained OB slices to record the simultaneous basal electrical activity of the rostral and caudal regions of the AOB and in presence of PRL. Results show that PRL promotes irregular estrous cycles and behavioral alterations. An increased olfactory preference for sociosexual stimuli was observed and altered sexual interaction, with more rejections towards the male and less stimulation received. Electrophysiological recordings in vitro showed a regional sensitivity for PRL in the electrical activity of the rostro caudal AOB population, making the caudal AOB more sensitive to PRL in spontaneous activity. However, this increase was prevented in hyperprolactinemic females. Overall, these results suggest that a hyperprolactinemic period during adulthood might promote a circuit reconfiguration within the AOB that changes the caudal response to PRL administration and could explain the behavioral responses.

Disclosures: B. Ordaz: None. **V. Viñuela-Berni:** None. **F. Pena:** None. **T. Morales:** None. **R. Corona:** None.

Poster

PSTR122: Pair Bonding and Sociability

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Program #/Poster #: PSTR122.15/E26

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: JSPS JP19K24681

Title: Posterior thalamic region implicating intralaminar nucleus are associated with social tactile process during social interaction in mice

Authors: *H. ARAKAWA;
Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: Maintaining prosocial interaction is essential for an adaptive life in all social species. Social interaction consists of sequential components of event-based actions, such as the detection of social cue, approach to a social stimulus, and subsequent touch/contact for assessing a social opponent. The neural circuits regulating represented behaviors in each phase require to cooperatively shape appropriate sequence of social interaction. In this context, social

touch/contact is a unique component that promotes switching the behavioral sequence from approach to contact-based interaction, and thus, establishing prosocial relationships. We hypothesized that the posterior thalamic nucleus, the posterior intralaminar nucleus (pIL) takes a role in relaying social tactile information to process contact-based interaction. The pIL sends projections to several limbic regions, including the paraventricular nucleus of the hypothalamus (PVN) and the medial amygdala (MeA). We found that c-Fos expression in the pIL neurons along with the PVN and MeA was exhibited by social encounters, and the pIL c-Fos level was more abundant in a direct physical encounter, while MeA c-Fos level was dominant in an indirect through grid encounter. Chemogenetic inhibition of pIL neurons, made by viral transfection of hM4Di, selectively reduced the investigatory approach and sniffing of a same-sex stimulus mouse in an indirect encounter setting. PIL inhibition had little impact on amount of direct social contacts but decreased the snout contact ratio in a direct encounter setting. Moreover, chemogenetic pIL inhibition had little effect on anxiety-like behavior in the elevated plus maze and body coordinative motor performance in the rotarod test. Interestingly, pIL inhibition induced tactile sense impairment evidenced by whisker sense-dependent gap crossing test and plantar touch tactile sense in Von Frey touch test. We discussed that the pIL and surrounding nuclei can process social tactile sensation and play a role in promoting prosocial interaction sequence and establishing prosocial relationships.

Disclosures: H. Arakawa: None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.16/E27

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: DI 039.350/2023 & DI 039.304/2023 PUCV

Title: Sexual dimorphisms on social behaviours of juvenile rats exposed early in life to antibiotics

Authors: *J. A. BRAVO[1], I. M. KUEHNEL[2], I. HERESMANN[3], C. E. GONZALEZ, Sr.[2], N. A. BAEZA[4], R. A. PARDO[5], M. JULIO-PIEPER[6];
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Química, Facultad de Ciencias, Valparaíso, Chile; [6]Inst. DE QUIMICA, PONTIFICIA Univ. CATOLICA DE VALPARAISO, VALPARAISO, Chile

Abstract: Background: Early life exposure to antibiotics (ELEA) has been shown to affect the mesocorticolimbic circuit in a sex-dependent manner, promoting addiction-like behaviours in adult male Sprague-Dawley rats, but not in females, while at the same time promoting neurochemical alterations in females but not in males (doi: 10.3389/fphar.2022.837652). These previous findings strongly suggest that this dopaminergic alterations could impact social behaviours. In addition, it has been shown that female oestrogen regulates dopamine levels and release, while oestrogen circulation is also regulated by the gut microbiota, thus contributing to the effects on the brain. Therefore, we asked if early-life acquisition of a gut microbiota exposed to wide spectrum non-absorbable antibiotics could impact social behaviours later in life, and to what extent do sex steroid contribute to these changes.
Aim: To evaluate whether ELEA diminishes social behaviour of rats, in a sex dependent manner.
Methods: ELEA was achieved through oral administration of a mixture of bacitracin, neomycin, vancomycin (100 mg/kg each) and pimaricin (5µg/kg) to pregnant Sprague-Dawley dams, from embrionary day 18 to postnatal day (PND) 7. The offspring of vehicle (VH) treated pregnant Sprague-Dawley dams served as controls. Behavioural analysis was carried out on male and female offspring on PND 35 to 37, where half of the subjects underwent gonadectomy (GDX), to remove the influence of sex steroids.
Results: ELEA did not affect weight gain in both males and females; however, it did increase the size of the caecum. In social behaviours, ELEA reduces pinning, pouncing and total time of social play, while it increases evasion compared to VH groups, with no sex distinction. In GDX males, ELEA diminishes entries and interaction time in the presence of an unknown rat compared to an empty cage. In the open field test, ELEA increased rearing behaviours in GDX males and sham operated females in comparison to VH GDX males and VH sham operated females respectively.
Conclusions: ELEA is capable of impairing social behaviours in rats, in a sex independent manner, while inducing changes in exploratory behaviours and hypervigilance in a sex dependent manner, thus suggesting a contribution of gut symbionts acquired early-life, on the establishment of social coping strategies for later in life.

Disclosures: J.A. Bravo: None. **I.M. Kuehnel:** None. **I. Heresmann:** None. **C.E. Gonzalez:** None. **N.A. Baeza:** None. **R.A. Pardo:** None. **M. Julio-Pieper:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.17/E28

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIMH- R01 MH121603

Title: Vasopressin 1a Receptor Cells in the Lateral Septum Code Social Investigation in Male Mice

Authors: *N. SCHAPPAUGH[1], A. ZAW[1], G. J. DE VRIES[2], A. PETRULIS[1];
[1]Georgia State Univ. Neurosci. Inst., Atlanta, GA; [2]Dept. of Biol., Georgia State Univ., Atlanta, GA

Abstract: The vasopressin (AVP)-expressing cells in the bed nucleus of the stria terminalis (BNST) represent one of the largest sex differences in the vertebrate brain. These cells have been shown to play a large role in male social investigation behavior, with much of this effect shown to be the result of AVP release into the lateral septum (LS), an area of the brain strongly expressing the vasopressin 1a receptor (V1aR). However, the nature of LS V1aR cell responsiveness to social cues is entirely unknown. To examine this issue, we used in vivo fiber photometry calcium imaging to measure changes in LS V1aR+ cell activity during social investigation (toward either caged male or female stimuli) in both male and female mice. In male mice, we found that V1aR cells in the intermediate LS increased their activity both during approach toward social stimuli and directly after termination of investigation, but showed reduced activity during social investigation itself. This pattern of response suggests that inhibition of LS V1aR cells may encode male social investigation, a finding that aligns with prior results. In females, however, these responses are absent, in line with previous findings that BNST AVP is not required for female social investigation. Although the LS expresses similar levels of V1aR between the sexes in mice, these cells may not encode social cues due to their reduced input from BNST AVP cells. These results lay the groundwork for understanding the network mechanisms underpinning the behavioral actions of sexually-differentiated AVP.

Disclosures: N. Schappaugh: None. **A. Zaw:** None. **G.J. De Vries:** None. **A. Petrulis:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.18/E29

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: The mechanism of social circuits dysfunction in ANK2-related ASD mice

Authors: *L. HE;
Xi'an Jiaotong Univ., Xi'an, China

Abstract: Male-specific urine scent-marking is a crucial social behavior for sexual and competitive advertisement. Mammals widely use this way to broadcast their pheromones to regulate the behavior of conspecifics. ANK2 is a high-functional autism spectrum disorder (ASD) gene. Specifically knocking out giant ankyrin-B (ankB), a neurospecific alternatively spliced variant of ANK2, will impair urine scent-marking behavior, but the circuits mechanism is still unknown. We first examined the expression of giant ankB in different brain area, and the

protein was enriched in stria terminalis(st), which was the tract contained the projections from the medial amygdala (MeA) to the bed nucleus of stria terminalis (BNST). Next, we assessed the expression of c-Fos in selected brain areas after the urine scent-marking behavior. It showed a higher level of cFos expression in these two areas. After that, we specifically knocked out giant ankyrin-B and found mice exhibited less urine marking. To further investigate this question, we recorded the electrophysiology data in MeA and BNST during the behavior, and abnormal firing was observed during this procedure. We then use chemical genetics methods to rescue the urine marking behavior in KO mice. Our results indicate the overactivation of MeA will cause the abnormal firing in BNST and reduce the urine marking behavior in ANK2-related ASD mice

Disclosures: L. He: None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.19/E30

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH RF1MH117070
NIH RF1MH126723
NIH T32HG000045
NIH 2T32GM007200-46
Autism Science Foundation

Title: Molecular-behavioral correlates of neurodevelopmental disorder-associated Myt1l mutation using single-nucleus genomics

Authors: *S. SARAFINOVSKA[1], A. YEN[2], D. SELMANOVIC[4], S. CHATURVEDI[5], J. D. DOUGHERTY[3];
[2]Genet., [1]Washington Univ. Sch. of Med., Saint Louis, MO; [3]Washington Univ. Sch. of Med., St. Louis, MO; [4]Washington Univ. in St. Louis, St Louis, MO; [5]Washington Univ. in St. Louis, St. Louis, MO

Abstract: Myelin transcription factor 1 like (MYT1L) is a neuron-specific transcription factor involved in the development and maintenance of postmitotic neurons. Disruptions in MYT1L lead to *MYT1L* Syndrome, a recently identified syndrome including autism, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability. Utilizing a *MYT1L* mutation identified in a local patient with *MYT1L* Syndrome, we generated heterozygous *Myt1l* mice (Hets) that recapitulated patient features including microcephaly, hyperactivity, and aberrant social motivation. Interestingly, the social motivation behaviors also displayed a sex bias. Our investigation of Hets' cortex revealed: a reduction in cell population due to insufficient expansion of neural progenitors, immaturity and disrupted electrophysiological activity in existing neurons, and disrupted gene expression.However, it is unclear if certain neuronal

subtypes are particularly susceptible to MYT1L loss and what are developmental windows during which MYT1L is indispensable. Knockout mice die immediately after birth, suggesting that this may be a critical period for MYT1L expression. To address this gap, we are performing single nucleus RNA sequencing (snRNAseq) on the frontal cortex of wildtype (WT) and Het mice immediately after birth, with the aim to understand how MYT1L loss impacts cellular proportions and gene expression patterns during this crucial developmental stage.One current obstacle in the field is determining transcriptional profiles that reflect individual behavioral phenotypes. To overcome this barrier, we are performing snRNAseq on hypothalamus in adult WT and Het mice immediately after completion of a social task. Specifically, we are leveraging a novel social motivation assay with which we have demonstrated that MYT1L genotype and sex significantly influence how much work a mouse will do for access to a social partner. We have also demonstrated MYT1L mice consistently exhibit hyperactivity in this and other assays. Sequencing immediately after the social motivation task will allow us to identify cellular proportions, gene expression profiles, and, uniquely, immediate early gene activation as a proxy for neuronal activity that can be associated with MYT1L loss, hyperactivity, and social motivation. Notably, we are also powered to identify sex-specific differences, highlighting potential interactions between MYT1L loss and sex. Overall, this research aims to uncover the molecular underpinnings of social motivation, autism, and ADHD-like phenotypes, ultimately paving the way for future targeted therapeutic strategies.

Disclosures: S. Sarafinovska: None. **A. Yen:** None. **D. Selmanovic:** None. **S. Chaturvedi:** None. **J.D. Dougherty:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.20/E31

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIMH R01-MH121603

Title: Potential Reciprocal Circuit Between Vasopressin Cells of the Bed Nucleus of the Stria Terminalis and Hypocretin Cells of the Lateral Hypothalamus

Authors: *A. ZAW[1], N. SCHAPPAUGH[1], G. J. DE VRIES[2], A. PETRULIS[1];
[1]Georgia State Univ. Neurosci. Inst., Atlanta, GA; [2]Dept. of Biol., Georgia State Univ., Atlanta, GA

Abstract: The vasopressin (AVP)-expressing cells of the bed nucleus of the stria terminalis (BNST) constitute one of the largest sources of sexually-differentiated vasopressin within the vertebrate brain. These cells project to many targets within the social decision/behavior network, including the lateral hypothalamus (LH). One of the cell populations within the LH that may influence social and emotional behavior are the hypocretin/orexin (Hcrt)-expressing cells, a

population noted for its strong effects on arousal. Here, using viral tracing, we demonstrate that BNST AVP cells project to the region of the LH where Hcrt+ cells are located and more so in males than females. Moreover, most of these cells express vasopressin receptor 1a (Avpr1a) mRNA, the primary receptor for AVP in the brain. These results suggest that some sexually-differentiated effects of brain vasopressin may be mediated by Hcrt+ cells. In addition, this connectivity appears to be bidirectional, as substantial amounts of Hcrt+ fibers are found surrounding BNST AVP cells. Together, our data suggest potential reciprocal interactions between sexually differentiated AVP and Hcrt-regulated arousal mechanisms.

Disclosures: A. Zaw: None. **N. Schappaugh:** None. **G.J. De Vries:** None. **A. Petrulis:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.21/E32

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Neurogenomic Consequences of Social Bonding on Chemosensory Circuits

Authors: E. BENTZ[1], L. L. SAILER[1], R. S. LASER[1], A. G. OPHIR[1], ***N. H. PRIOR**[2]; [1]Psychology, [2]Cornell Univ., Ithaca, NY

Abstract: Social bonding produces long-term impacts on an individual's brain and behavior. Most research on the neurobiology of pair bonding focuses on a small number of key brain regions (especially the Nucleus Accumbens) and changes that occur early in social bonding. In contrast, the neurobiological and genomic mechanisms that support enduring changes associated with social bonding are poorly understood. Chemosensory signals are integral to rodent social behavior but are rarely included in neurobiological investigations of pair bonding. Furthermore, we hypothesized that pair bonding would induce chromatin remodeling, a molecular mechanism producing large-scale changes to transcriptional regulation, in chemosensory circuits. Here, we leveraged the well-studied prairie vole (M*icrotus ochrogaster)* system in order to: 1) compare the neurogenomic consequences (RNAseq) of long-term bonds on chemosensory and social-decision making networks (SDMN), and 2) test whether pair bonding induces changes in chromatin structure within chemosensory circuits. In this study, we compared same sex dyads with monogamous partners that had been housed together for longer than 2 months and allowed to breed. In general the effects of social bonding on neurogenomic state were distributed throughout the SDMN, chemosensory circuits, and peripheral chemosensory tissues. However, in both males and females, the regions with the most differentially expressed genes (DEGs) were sensory cortices: the olfactory bulb and the auxiliary olfactory bulb. From our dataset, we also found that DEGs were enriched for functions associated with chromatin remodeling and post-transcriptional mRNA processing. Currently, we are describing chromatin accessibility using ATAC-seq in the auxillary olfactory bulb. This study provides an exciting line of evidence highlighting the involvement of chemosensory circuits in long-term social bonding.

Disclosures: E. Bentz: None. **L.L. Sailer:** None. **R.S. Laser:** None. **A.G. Ophir:** None. **N.H. Prior:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.22/E33

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Research Apprentice Program - Christopher Newport University
Summer Scholars Program - Christopher Newport University

Title: Zebrafish (Danio rerio) can use visual-only cues to detect conspecifics' response to the synthenthetic alarm substance hypoxanthine-3N-oxide ($C_5H_4N_4O_2$).

Authors: *A. J. VELKEY, II[1], K. KINSLOW[6], M. BOWERS[2], E. HOFFMAN[2], B. SURISETTY[2], J. MARTIN[1], J. J. KANAPALA[2], R. CATERBONE[3], T. J. KIRCHOFF[2], M. E. DWYER[4], S. J. WILLIAMS[5];
[1]Neurosci. Program, [2]Mol. Biol. and Chem., [3]Mo, [4]Organismal and Envrn. Biol., [5]Psychology, Christopher Newport Univ., Newport News, VA; [6]Neurosci. Program, Christopher Newport Universisty, Newport News, VA

Abstract: Zebrafish (*Danio rerio*), a common model organism in behavioral neuroscience, have a complex repertoire of social behaviors, including shoaling. Shoaling is seen when members of a group of fish congregate loosely with each other with little synchrony in movement across group members. Previous research has shown that zebrafish prefer an established social environment and that zebrafish are able to detect subtle movement differences among group members. These findings have been confirmed in several studies using the three-chamber Open-Tank Free-Swim Task (OTFST). In the present study using the OTFST, single subjects in the center tank were provided simultaneous visual exposure to a small shoal (n = 4) exposed to synthetic alarm substance (1.5 nM $C_5H_4N_4O_2$) in one flanking tank and another small shoal (n = 4) that remained unalarmed in the other flanking tank. The movement of each subject in the center tank was digitally recorded during a single session using MediaRecorder; videos were subsequently analyzed using EthoVision XT 15. Three distinct behavioral syndromes were noted in the aggregated response tracks among sub-groups of subjects; while some subjects exhibited social contagion and other subjects exhibited social buffering during their respective sessions, a separate group exhibited boldness throughout their sessions. Collectively, female subjects exhibited lower levels of behavioral entropy, spending more time in the bottom quadrant of the tank in proximity with the unalarmed shoal and less time in proximity with the alarmed shoal while male subjects exhibited higher levels of behavioral entropy while demonstrating similar response profiles. This study promises to advance the understanding of mechanisms that produce distinct social behaviors and anti-predation responses in zebrafish.

Disclosures: A.J. Velkey: None. **K. Kinslow:** 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 Apprentice Program - Christopher Newport University. **M. Bowers:** None. **E. Hoffman:** None. **B. Surisetty:** 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.; Summer Scholars Program - Christopher Newport University. **J. Martin:** 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 Apprentice Program. **J.J. Kanapala:** None. **R. Caterbone:** None. **T.J. Kirchoff:** None. **M.E. Dwyer:** None. **S.J. Williams:** None.

Poster

PSTR122: Pair Bonding and Sociability

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR122.23/E34

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant AG070377

Title: Differential effects of Oxtr signaling on pair bonding with age

Authors: D. MANOLI[1], **K. BERENDZEN**[2];
[1]Psychiatry, Univ. of California San Francisco, San Francisco, CA; [2]Univ. of California San Francisco, San Francisco, CA

Abstract: Social relationships are increasingly recognized to have a profound influence on human health. Social isolation and loss of social attachments have been associated with increased risk of numerous adverse health outcomes, including cardiovascular disease, diabetes, and all-cause mortality. Neuroendocrine signaling, particularly oxytocin signaling, is implicated in regulating organ and tissue function throughout the lifespan and is a known mediator of attachment behavior across species. However, a mechanistic understanding of how oxytocin regulates the links between social attachment behavior and peripheral physiological health is unclear, and has been limited by the lack of genetic animal models displaying long-term adult social bonds. The prairie vole is a unique rodent species that exhibits life-long pair bonds, making it an ideal model system by which to study attachment. We have adapted molecular genetic tools to the prairie vole, allowing us to generate mutations in genes of interest, including the oxytocin receptor (*Oxtr*). Using this system, we found that loss of Oxtr signaling delays formation of adult pair bonds and leads to distinct changes in transcriptional signatures in brain regions implicated in attachment and other social behaviors. Using RNA-Seq from brain samples from WT and *Oxtr-/-* voles, we identified baseline differences in gene expression in the nucleus

accumbens due to loss of *Oxtr*. Pathway analysis implicates known oxytocin receptor signaling genes, as well as genes related to other GPCR and non-neuronal signaling pathways. Further, oxytocin receptors are expressed throughout the body, in multiple organ systems, regulating cardiovascular and metabolic function, fluid homeostasis, and food intake. Our overarching hypothesis is that oxytocin signaling is required for the broad physiological benefits associated with social attachment and regulates peripheral physiological changes with pair bonding across the lifespan. Functional changes with social attachment or social stressors may reflect mechanisms of resilience or vulnerability respectively in physiological systems regulated by oxytocin. Thus, we aim to clarify the role of oxytocin signaling in coordinating function across physiological systems and social states throughout the lifespan.

Disclosures: D. Manoli: None. **K. Berendzen:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.01/E35

Topic: F.03. Stress and the Brain

Support: Korea Ginseng Corp

Title: American ginseng (Panax quinquefolius) extracts (G1899) reverse stress-induced behavioral abnormalities

Authors: *M. WILES[1], R. LEE[1], E. BOUCKOVA[1], M. WUSTRAU[1], J. FLOWERS[1], P. VETTER[1], J. LEE[2], B. HAN[2], S. KIM[1];
[1]Colorado State Univ., Fort Collins, CO; [2]Korea Ginseng Corp, Gwacheon-si, Korea, Republic of

Abstract: Chronic stress affects brain functions, which leads to the development of mental disorders like anxiety, depression, cognitive decline, and social dysfunction. There is increasing focus on the role of nutritional, herbal and nutraceutical compounds on mental and cognitive functioning. Interestingly, studies suggest that American ginseng (Panax quinquefolius) extracts (G1899) improve cognition. We thus examined whether G1899 showed protective effects on stress-induced behavioral changes in animals. 250 mg/kg G1899 was orally delivered daily for 4 weeks to 2-month-old female and male mice before inducing stress. To induce acute stress in animals, we intraperitoneally injected a low dose of lipopolysaccharides (LPS) (10 μg/kg), and saline was used as a control. After LPS injection, multiple behavioral assays were carried out - a sucrose preference test, an open filed test, reciprocal social interaction, contextual fear conditioning, and a tail suspension test - to determine whether LPS-induced stress affected animals' behaviors and whether G1899 had protective effects against stress. We found that G1899 reversed stress-indued behavioral abnormalities including depression-like behavior, anhedonia, social dysfunction, and fear memory impairments in both females and males. Our

study suggests that G1899 supplement can be protective against LPS-induced acute stress in animals.

Disclosures: M. Wiles: None. **R. Lee:** None. **E. Bouckova:** None. **M. Wustrau:** None. **J. flowers:** None. **P. Vetter:** None. **J. Lee:** A. Employment/Salary (full or part-time):; Korea Ginseng Corp. **B. han:** A. Employment/Salary (full or part-time):; Korea Ginseng Corp. **S. Kim:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Korea Ginseng Corp..

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.02/E36

Topic: F.03. Stress and the Brain

Support: Colorado State University
Korea Ginseng Corp.

Title: Ketamine reverses chronic stress-induced mental disorders via the expression of Ca^{2+}-permeable AMPA receptors in mice

Authors: *J. FLOWERS[1], P. E. VETTER[2], E. BOUCKOVA[2], M. J. WILES[2], M. H. WUSTRAU[2], R. LEE[2], S. KIM[2];
[1]Colorado State Univ. Mol., Cell. & Integrative Neurosciences, Fort Collins, CO; [2]Colorado State Univ., Fort Collins, CO

Abstract: Both preclinical and clinical studies demonstrate that chronic stress reduces AMPA Receptor (AMPAR) subunit GluA1 levels in hippocampal synapses, while there are conflicting results describing alterations in hippocampal GluA2 levels under chronic stress. These results suggest that the stress-induced decrease in hippocampal GluA1 levels is correlated with both weakened excitatory synaptic transmission and altered hippocampus-dependent behaviors in chronic stress. Importantly, we have revealed that low-dose ketamine rapidly induces the expression of GluA1- containing, GluA2-lacking Ca^{2+}-Permeable AMPARs (CP-AMPARs), a subtype of AMPARs that have larger single channel conductance, in the hippocampus. We have further shown that this ketamine-induced CP-AMPAR expression enhances glutamatergic synaptic strength in hippocampal neurons, which allows animals to exhibit less anxiety- and depression-like behaviors. Our new findings further demonstrate that low-dose ketamine treatment can reverse disruptions in hippocampus-dependent fear memory and social behavior caused by chronic restraint stress (CRS) in mice. Research also shows that ketamine-induced restoration of impairments of AMPAR-mediated synaptic transmission and behaviors in stressed animals is associated with an increase in synaptic GluA1 expression in the hippocampus. Notably, the hippocampus is one of the key brain regions controlling social behavior and

learning and memory. Moreover, an increase in hippocampal activity reverses stress-induced memory impairment, social dysfunction, and mood disorder-linked behaviors. More importantly, a recent study shows that the hippocampus is selectively targeted by low-dose ketamine. These existing data and our findings show that ketamine at the low dose rapidly induces the expression of CP-AMPARs in the hippocampus, which in turn enhances synaptic strength to reverse hippocampus-dependent behavioral dysfunctions in chronically stressed animals.

Disclosures: J. flowers: None. **P.E. Vetter:** None. **E. Bouckova:** None. **M.J. Wiles:** None. **M.H. Wustrau:** None. **R. Lee:** None. **S. Kim:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Korea Ginseng Corp.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.03/E37

Topic: F.03. Stress and the Brain

Title: Visual EMDR Stimulation Mitigates Acute Varied Stress Effects on Morphology of Hippocampal Neurons in Male Wistar Rats

Authors: Y. RUVALCABA DELGADILLO[1], D. MARTÍNEZ FERNÁNDEZ[2], M. S. LUQUIN DE ANDA[3], D. REDOLAR-RIPOLL[4], F. JAUREGUI[5], *D. FERNÁNDEZ-QUEZADA[6];
[1]Neurosci., Univ. De Guadalajara, Zapopan, Mexico; [2]Farmacobiología, Univ. of Guadalajara, Guadalajara, Mexico; [3]Univ. of Guadalajara, Guadalajara, Mexico; [4]Psychology and Educational Sci., Univ. Oberta De Catalunya, Barcelona, Spain; [5]Lab. de Fisiología del Comportamiento UNAM, Guadalajara, Mexico; [6]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Stress is a pervasive health concern known to induce physiological changes, particularly impacting the vulnerable hippocampus and the morphological integrity of its main residing cells, the hippocampal neurons. Eye Movement Desensitization and Reprocessing (EMDR), initially developed to alleviate emotional distress, has emerged as a potential therapeutic/preventive intervention for other stress-related disorders. This study aimed to investigate the impact of Acute Variable Stress (AVS) on hippocampal neurons and the potential protective effects of EMDR. Rats were exposed to diverse stressors for 7 days, followed by dendritic morphology assessment of hippocampal neurons using Golgi-Cox staining. AVS resulted in significant dendritic atrophy, evidenced by reduced dendritic branches and length. In contrast, rats receiving EMDR treatment alongside stress exposure exhibited preserved dendritic morphology comparable to controls, suggesting EMDR's protective role against stress-induced dendritic remodeling. These findings highlight the potential of EMDR as a neuroprotective intervention in mitigating stress-related hippocampal alterations.

Disclosures: Y. Ruvalcaba Delgadillo: None. **D. Martínez Fernández:** None. **M.S. Luquin de Anda:** None. **D. Redolar-Ripoll:** None. **F. Jauregui:** None. **D. Fernández-Quezada:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

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Program #/Poster #: PSTR123.04/E38

Topic: G.04. Emotion

Support: CSTB2022NSCQ-MSX1304

Title: Red Blood Cell Membrane Camouflaging Nanodrugs Penetrate Blood-Brain Barrier for Enhanced Depression Therapy

Authors: *Z. LAN[1], W. LI[2];
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Abstract: Depression is a leading cause of disability and suicide, contributing significantly to the global burden of disease. However, current treatments for depression often require oral administration of high-dose antidepressants over weeks or months to produce noticeable antidepressant effects. Thus, there is an urgent need for improved therapeutics that can reduce the time required to achieve antidepressant effects while minimizing hepatorenal toxicity. The solution lies in developing an effective delivery platform to facilitate drug penetration across the blood-brain barrier (BBB) for precise drug delivery. In this study, we use bionics principle to develop a smart nanocarrier by loading the antidepressant fluoxetine into the red blood cell (RBC) membrane nanovesicles. This biomimetic nanomedicine could extend the blood circulation time of drugs in mice and improve the BBB penetration efficiency through targeting peptides, thereby improving the therapeutic effect of antidepressant drugs with reduced toxicity. Moreover, *in vitro* and *in vivo* studies showed that fluoxetine-loaded RBC delivery system held favorable BBB penetration capability and reliable biocompatibility. It is worth mentioning that the delivery system also performed a pivotal role in balancing glucose metabolism, which was thus capable of scavenging depression-induced reductions in glucose metabolism in brain areas. Subsequently, behavioral and biochemical experiments also demonstrated significant depression-ameliorating effects in vivo. In summary, for the first time, we have demonstrated the therapeutic effect of a fluoxetine-loaded RBC delivery system for enhanced depression therapy. Compared with free fluoxetine, this biomimetic nanocarrier can improve the therapeutic efficiency of antidepressant drugs and greatly shorten the therapy time for depression, which has great potential for clinical application in the future.

Disclosures: Z. Lan: None. **W. Li:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.05/E39

Topic: G.05. Mood Disorders

Support: NIDA Grant DA000522-16
Tactogen PBC

Title: Stereoisomers of 5-(2-methylaminobutyl)benzofuran (5-MABB) exhibit differential effects on monoamine transporter activity and physiological parameters in rats

Authors: A. D. MAITLAND[1], D. WALTHER[1], M. J. BAGGOTT[2], *M. H. BAUMANN[1]; [1]IRP, NIDA, NIH, Baltimore, MD; [2]Tactogen Inc, Redwood City, CA

Abstract: 3,4-Methylenedioxymethamphetamine (MDMA, or “Ecstasy”) is a proposed pharmacotherapy for treating post-traumatic stress disorder. MDMA acts as a monoamine releasing agent at transporters for 5-HT (SERT), norepinephrine (NET), and dopamine (DAT). Therapeutic effects of MDMA are presumably mediated by 5-HT release at SERT, whereas adverse effects like cardiovascular stimulation and abuse liability involve release at NET and DAT. Thus, there is interest in developing MDMA-like drugs with a better side-effects profile. Here we investigated the biological effects of benzofuran analogs that act as MDMA-like monoamine releasing agents. Stereoisomers of 5-(2-methylaminopropyl)benzofuran (5-MAPB) and 5-(2-methylaminobutyl)benzofuran (5-MABB) were pharmacologically characterized using *in vitro* and *in vivo* methods. Effects of the compounds on uptake inhibition and release at SERT, NET, and DAT were carried out in female rat brain synaptosomes. Physiological effects of s.c. drug administration were measured in six female Sprague-Dawley rats fitted with surgically implanted telemetric transponders sensitive to blood pressure (BP), heart rate (HR), motor activity, and body temperature. *In vitro* assay results revealed that stereoisomers of 5-MAPB and 5-MABB fully inhibited uptake at monoamine transporters. R- and S-5-MAPB were also fully efficacious releasing agents at SERT, NET, and DAT, similar to MDMA. S-5-MABB displayed fully efficacious release at all transporters, whereas R-5-MABB displayed hybrid transporter activity characterized by fully efficacious release at SERT, partial release at NET, and no release at DAT. *In vivo* telemetry results showed that stereoisomers of 5-MAPB (0.3-3.0 mg/kg) and 5-MABB (1.0-10 mg/kg) stimulated BP, but the magnitude of the effect was reduced compared to MDMA (1.0-10 mg/kg). S-5-MAPB increased motor activity similar to MDMA but other compounds were less efficacious. All drugs, with the exception of S-5-MAPB, decreased body temperature. These drugs have MDMA-like effects on BP and activity, but certain stereoisomers have less potent and less efficacious effects on cardiovascular stimulation and locomotor activity. Taken together, the present results demonstrate that R-5-MABB displays hybrid transporter activity, with reduced releasing actions at NET and DAT, but fully efficacious release at SERT. The unique transporter activity of R-5-MABB is accompanied by reduced cardiovascular and motor stimulation, suggesting a safer profile of adverse effects when compared to MDMA.

Disclosures: A.D. Maitland: None. **D. Walther:** None. **M.J. Baggott:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **M.H. Baumann:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.06/E40

Topic: G.05. Mood Disorders

Support: Tactogen Inc.

Title: Preliminary characterization of TACT833, a novel MDMA-like benzofuran derivative.

Authors: R. L. BURROUGHS[1], C. JOHNSON[2], S. KALLAKURI[3], D. WALTHER[4], L. E. BAKER[5], *S. PERRINE[6], M. H. BAUMANN[7], **M. J. BAGGOTT**[8];
[1]Western Michigan Univ., Kalamazoo, MI; [2]WMU, Mattawan, MI; [3]Psychiatry and Behavioral Neurosci., Wayne State Univ., Detroit, MI; [4]NIH, Bethesda, MD; [5]Psychology, Western Michigan Univ., Kalamazoo, MI; [6]Wayne State Univ., Detroit, MI; [7]Designer Drug Res. Unit, IRP, NIDA, NIH, Baltimore, MD; [8]Tactogen Inc, Redwood City, CA

Abstract: Background and Aims: MDMA is a proposed pharmacotherapy adjunct for the treatment of PTSD and other disorders. High or repeated doses of MDMA can cause long-term decreases in markers of serotonergic functioning, which have been linked to subacute mood lowering and long-term loss of MDMA's therapeutic efficacy. We sought to develop a novel benzofuran derivative that retained MDMA's therapeutic effects while lacking its long-term adverse effects on the serotonin system. **Methods**: To identify in vivo MDMA-like effects we used a drug discrimination paradigm in which TACT833 was administered to male Sprague-Dawley (SD) rats that had been trained to discriminate MDMA (1.5 mg/kg, I.P., 15 min) under an FR 20 schedule of food reinforcement. TACT833 (1.35 and 4.05 mg/kg IP) was further screened for antidepressant-like residual effects using the forced swim test (FST). Potential long-term serotonin depletions were assessed in the striatum, frontal cortex, and hippocampus at 2 weeks after 6.75 mg/kg x 3, every 2 hrs. *In vitro* pharmacology was characterized against a panel of 47 potential targets with concentrations up to 30 µM. Effects on uptake inhibition and release at SERT, NET, and DAT were assessed using rat brain synaptosomes. **Results:** TACT833 dose-dependently substituted for MDMA in the drug discrimination task, but, unlike MDMA, did not produce long-term serotonin depletions after a repeated dose regimen. TACT833 had dose-dependent antidepressant-like effects in FST at post-24 hours, with the higher dose decreasing and increasing mobility and swimming time, respectively, without affecting climbing or diving. Synaptosome uptake and release assays indicated that TACT833 is a full substrate-type releaser of 5-HT and NE and a partial releaser of DA, with EC_{50}s below 400 nM. In addition, it acts as a 5-HT_{1B} receptor agonist (EC_{50} 107 nM). **Conclusions:** TACT833 is a promising novel

compound that may share the therapeutic effects of MDMA with minimal serotonin-lowering effects.

Disclosures: R.L. Burroughs: 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.; Tactogen. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **C. Johnson:** 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.; Tactogen. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **S. Kallakuri:** A. Employment/Salary (full or part-time):; Tactogen. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **D. Walther:** None. **L.E. Baker:** 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.; Tactogen. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **S. Perrine:** 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.; Tactogen. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Tactogen. **M.H. Baumann:** None. **M.J. Baggott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactogen.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.07/F1

Topic: G.05. Mood Disorders

Support: NIMH Grant 1R01MH130658
MindMed Inc

Title: Dissecting the acute effects of MDMA on behavior

Authors: *J. GUARDADO[1], A. AMILCAR[2], A. CLEMENTS[3], R. YAN[5], D. LIN[6], T. SIPPY[4]; [1]New York Univ. Sch. of Med., New York, NY; [2]Systems Neurosci., New York Univ., New York, NY; [3]New York Univ., Lakeland, FL; [4]New York Univ., New York, NY; [5]New York Univ. Langone Med. Ctr., New York, NY; [6]New York Univ. Neurosci. & Physiol., New York, NY

Abstract: 3,4-Methylenedioxymethamphetamine (MDMA)-Assisted Therapy (**MDMA-AT**) is rapidly being established as an effective treatment for PTSD, possibly outperforming established pharmacological alternatives. MDMA is considered an empathogenic drug, and its prosocial properties are thought to facilitate patient-therapist interactions and lessen anxiety as well as emotional impacts of trauma. However, it is well recognized that the drug can induce anxiety when used recreationally and therapeutically. These mixed reports likely stem from the differential time course of action that MDMA has on distinct neuromodulator systems, as well as the influence of environmental context on the effects of the drug. We hypothesized that context and time after MDMA administration are factors that can influence the MDMA-induced behavioral profile in mice. To test the effect of social context, we employed a battery of behavioral assays the three-chamber test (3CT), two cup test (2CT), a freely moving social interaction assay (SI) and the resident-intruder (RI) test. We found that MDMA did not significantly affect social investigation in the 3CT. Only when both animals are dosed in the 2CT do we see an increase in social investigation. However, the SI assay revealed less social investigation overall, even with both animals dosed. Finally, in a well-established resident intruder task, MDMA reduced aggression in the intruder (aggressor mouse), while having no effect on other types of social investigation. This data demonstrates that altering the context can change the way MDMA influences social behavior. To reveal the temporal dynamics of MDMA-induced effects, we used depth motion sequencing (Moseq) to automatically cluster stereotyped behavioral motifs over 2 hours in freely moving mice. The model identified several freeze-, rear-, groom-, and dash-like behaviors that we could jointly analyze for anxiety-like and hyperactive effects of the drug, compared to saline controls. Dosed animals show more freezing and avoidance of the center, which was time dependent. They also show less grooming, rearing, and active exploration, and increased dashing. Overall, our data reveals that the effect of MDMA on mice is highly varied due to context and time. This work is both timely and impactful, as MDMA is likely to be a mainstay in treatment for PTSD. Establishing behavioral and biological biomarkers in mice that relate to the effects of MDMA in humans will allow us to better understand the neural circuit mechanisms underlying the therapeutic effects of this highly complex, yet promising drug.

Disclosures: J. Guardado: None. **A. Amilcar:** None. **A. Clements:** None. **R. Yan:** None. **D. Lin:** None. **T. Sippy:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.08/F2

Topic: G.05. Mood Disorders

Title: Hesperidin Mitigates Maternal Separation Stress-Induced Neuropsychiatric Disorders in Mice: Behavioural and Biochemical Evidences

Authors: *V. SINGH;
Dept. of Pharmaceut. Sci. and Technol., Maharaja Ranjit Singh Punjab Tech. Univ., Bathinda, India

Abstract: Early-life maternal separation stress (MSS) has been shown to induce significant emotional and behavioral changes, with enduring consequences on neurodevelopment and mental health in adulthood. This study aims to investigate the neurotherapeutic potential of hesperidin, a natural flavonoid, in mitigating the long-term effects of MSS on neurobehavioral outcomes in mice. To induce MSS, pups were separated from their mothers for three hours daily from Postnatal Day (PND) 2 to PND 14, followed by reunification until PND 21. After weaning, the pups were housed until PND 60. Upon reaching PND 60, hesperidin was administered at doses of 20 and 40 mg/kg for 15 consecutive days until PND 75. On PND 75, a battery of behavioral tests was conducted to assess psychiatric (forced swim test and elevated plus maze) and cognitive (passive shock avoidance task and Morris Water Maze) comorbidities, followed by biochemical analysis of the cortex and hippocampus to evaluate oxidative stress, neuroinflammation, and apoptosis. Animals exposed to early-life MSS exhibited depressive-like behavior, anxiety-like behavior, and cognitive impairments, all of which were significantly ameliorated by chronic treatment with hesperidin at doses of 20 and 40 mg/kg. Furthermore, hesperidin administration restored circulating corticosterone levels, brain oxidative stress markers (glutathione, TBARS, myeloperoxidase and Nrf2), pro-inflammatory cytokines (TNF-α, IL-6 and NF-κB) and apoptotic marker (caspase-3) in the hippocampus and cortex of MSS-exposed animals. These findings underscore the neuroprotective effects of hesperidin against MSS-induced neuropsychiatric disorders and suggest its potential as a therapeutic intervention for mitigating the long-term consequences of early-life stress on brain development and function.

Disclosures: V. Singh: None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.09/F3

Topic: G.05. Mood Disorders

Support: 5R21MH128574-02

Title: Glyoxalase I inhibitors: novel insights in the fast-acting antidepressant effects following chronic stress

Authors: *A.-J. LEE[1], C. BUI[1], M. ULIVIERI[2], X. FAN[3], H. ROSBERG[4], S. C. DULAWA[5];
[2]Psychiatry, [1]UC San Diego, La Jolla, CA; [3]Univ. of California San Diego, La Jolla, CA; [4]Psychiatry, UCSD, San Diego, CA; [5]Psychiatry, Univ. of California - San Diego, La Jolla, CA

Abstract: Depression is a complex mood disorder affecting millions of people worldwide. Common medications require weeks to show efficacy and ≈40% of patients are treatment

resistant. Ketamine, the only fast-acting antidepressant compound currently clinically approved, is still ineffective in ≈30% of patients. We previously demonstrated that 5-days Glyoxalase I (Glo1) inhibitors treatment induces antidepressant effects following chronic mild stress (CMS), by reducing the catabolism of methylglyoxal (MG), an endogenous GABAA partial agonist. We here investigate fast-acting antidepressant effects of methylgerfylin (MeGFN), a Glo1 inhibitor, with behavioral and neuronal activity (fiber photometry, FP) studies in wild-type animals and animals carrying the human Val66Met polymorphism for BDNF. Following 6-weeks of chronic mild stress, male and female Balb/c mice received MeGFN, ketamine (fast-acting antidepressant control group) or their respective vehicle. Animals are then tested in a battery of behavioral tests resembling depressive behaviors: frustration induced by reward omission, effort-related choice (ERC), social interaction, coat state, open field, forced swim test (FST). We found that acute injection of MeGFN following CMS is able to ameliorate coat state deterioration and FST immobility time within 24 hours, without affecting locomotor activity; Glo1 inhibition also restores reduced sociability. Moreover, we show the impact of CMS on frustration induced by reward omission and ERC. Most importantly, we performed the same protocol in mice carrying either heterozygous or homozygous polymorphism of BDNF Val66Met, which has been linked to alteration of activity-dependent BDNF release. The presence of Met/Met genotype determines the absence of activity-dependent BDNF release and depressed humans harboring this genotype show a poor response to ketamine's antidepressant effects. Through this study we introduce a novel antidepressant effect mediated by Glo1 inhibition. Lastly, by performing multispectral recording of projections from the prefrontal cortex to the lateral habenula and habenular neurons, our preliminary studies show the effects of Glo1 inhibition in modulating cortico-habenular pathway. Overall, our study demonstrates that Glo1 inhibition is a potential novel antidepressant mechanism with fast-acting properties.

Disclosures: A. Lee: None. **C. Bui:** None. **M. Ulivieri:** None. **X. Fan:** None. **H. Rosberg:** None. **S.C. Dulawa:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.10/F4

Topic: G.05. Mood Disorders

Support: NSTC 110-2320-B-039-028-MY3
NSTC 109-2320-B-039-020
NSTC 108-2320-B-039 -015
CMU CMU109-MF-80

Title: Pparα Activation through treatment of osthole alleviates repeated social defeat stress induced maladaptive behaviors in mice

Authors: *C.-W. CHEN[1], C. LIN[2], L.-Y. YANG[2], D.-Y. LU[3];
[1]Inst. of Translational Med. and New Drug Develop., [2]Dept. of Physiology, Sch. of Med., [3]Dept. of Pharmacology, Sch. of Med., China Med. Univ., Taichung, Taiwan

Abstract: Psychosocial stress may induce neuroinflammatory responses, which are associated with the pathogenesis of various psychiatric disorders, such as anxiety disorders and depression. Osthole—a natural coumarin extracted from the seeds of the Chinese herb *Cnidium monnieri*—exerts anti-inflammatory and antioxidative actions on the central nervous system. However, the neuroprotective benefits of osthole against psychiatric disorders remain largely unclear. In previous study, mice subjected to repeated social defeat stress (RSDS), a well-established rodent model of anxiety disorder, in the presence of aggressor mice exhibited social avoidance and anxiety-like behaviors. In this study, we investigated the neuroprotective effects of osthole and the underlying molecular mechanisms. We found osthole exerted therapeutic effects on cognitive behaviors, mitigating anxiety-like behaviors and social avoidance in a mouse model of RSDS. The anti-inflammatory response enhanced by the oral administration of osthole was strengthened through the upregulation of heme oxygenase-1 expression. Peroxisome proliferator-activated receptor α (PPARα) expression was repressed in mice subjected to RSDS. Nonetheless, osthole treatment reversed the suppression of PPARα expression. We further identified a positive correlation between heme oxygenase-1 expression and PPARα expression in osthole-treated mice. Taken together, osthole may be developed as a novel medicine for mood disorders. Importantly, targeting the activation of PPARα should be considered when developing potential drugs for psychiatric disorders.
Keywords: social defeat stress; social avoidance; anxiety-like behaviors; PPARα; HO-1

Disclosures: C. Chen: None. **C. Lin:** None. **L. Yang:** None. **D. Lu:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.11/F5

Topic: G.05. Mood Disorders

Title: Intranasal delivery of lumbrokinase improves chronic social defeat stress-induced behavioral abnormalities in mice

Authors: *V. CHAROENSAENSUK[1], L.-Y. YANG[2], D.-Y. LU[1];
[1]Pharmacol., [2]Physiology, Sch. of Med., China Med. Univ., Taichung, Taiwan

Abstract: Brain-derived neurotrophic factor (BDNF), particularly the mature form (mBDNF), plays a pivotal role in the pathogenesis of psychological disorders. mBDNF binds to its receptor, tropomyosin-related kinase B (TrkB), and activates BDNF-TrkB signaling cascades that promote neuron survival and neuroplasticity. Fibrinolytic enzymes, including tissue plasminogen activator (tPA), have been reported to regulate proteolytic maturation of BDNF. Lumbrokinase

extracted from earthworms is a member of proteolytic enzymes, which include plasminogen activator. Lumbrokinase has been widely used to treat cardiovascular disease and stroke. However, the effects of lumbrokinase on psychological disorders remain to be investigated. In this study, we examined whether lumbrokinase rescued chronic stress-associated maladaptive behaviors through modulation of tPA/BDNF pathways. Male C57BL/6 mice underwent chronic social defeat stress (CSDS) paradigm for ten consecutive days to induce behavioral impairments. Following CSDS, a social interaction test was performed to separate resilient and susceptible mice. Lumbrokinase was administered to the susceptible mice through the intranasal route (INA). Our results showed that lumbrokinase significantly improved CSDS-elicited social avoidance and anxiety-like behaviors in mice, as manifested by social interaction and open field tests. Moreover, we found that CSDS mice expressed lower tPA and mBDNF levels in their hippocampus compared to the control mice. Importantly, treatment with lumbrokinase significantly reversed the phenomenon. In conclusion, this study demonstrated the therapeutic effects of lumbrokinase against CSDS-induced maladaptive behaviors in mice. Lumbrokinase promotes the expression of tPA, thus increasing the maturation of BDNF that contributes to their protective effect in CSDS-induced behavioral deficit.

Disclosures: V. Charoensaensuk: None. **L. Yang:** None. **D. Lu:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.12/F6

Topic: G.05. Mood Disorders

Title: Beta-caryophyllene reduces anxiety and depression and improves spatial memory in mice exposed to unpredictable mild stress

Authors: *K. D. PARFITT, S. J. DONOVAN;
Neurosci., Pomona Col., Claremont, CA

Abstract: Anxiety and depressive disorders, often exacerbated by stress, are the most common classes of psychiatric disorders in the world. Conventional treatments, predominantly benzodiazepines, SSRIs, and SNRIs offer moderate efficacy and are frequently hampered by interactions with other medications and delayed therapeutic responses. β-caryophyllene (BCP), a non-psychoactive terpene from the cannabis plant, produces very mild psychoactive effects and has been shown to have a high selectivity for cannabinoid type II receptors (CB2Rs). In the present study we hypothesized that BCP would exhibit significant anxiolytic, antidepressant, and cognitive-enhancing effects in both stressed and unstressed C57Bl6 mice. To test this, we examined the effects of a single injection of BCP (50 mg/kg, i.p) on performance in the Elevated Plus Maze (EPM), Open Field Test (OFT), Tail Suspension Test (TST), Morris Water Maze (MWM), and Y-Maze, in stressed and unstressed male and female C57BL/6 mice. Assays were conducted after 2-3 unpredictable mild stressors (UMS) per day for 3 weeks prior to and on the

day of behavioral testing. Our results demonstrated that BCP treatment significantly increased time spent in the open arms in both stressed mice ($p < 0.05$; one-way ANOVA and Tukey's post-hoc analysis) and unstressed mice ($p < 0.01$), with no observable change in locomotor activity, suggesting a strong anxiolytic effect. The cannabinoid treatment also increased the time in the bright center of the OFT in both stressed and unstressed mice ($p<0.05$). In the TST, BCP treatment consistently reduced immobility times in both the stressed and unstressed mice ($p < 0.05$), indicative of antidepressant properties. Notably, BCP significantly enhanced long-term spatial memory in the MWM in stressed and non-stressed mice, evidenced by increased platform zone crossovers during probe trials($p<0.05$), without affecting total distance traveled. BCP did not, however, influence short-term spatial working memory in the Y-Maze spontaneous alternation task, suggesting that its cognitive effects might be task-specific or influenced by different underlying mechanisms than those affecting longer-term memory processes. Taken together, these results strongly support BCP's potential as a multifaceted therapeutic agent, offering benefits for the treatment of anxiety, depression, and cognitive impairments. Future work should involve exploration of the molecular mechanisms of BCP's action, optimal dosing strategies, and examination of long-term safety profiles.

Disclosures: K.D. Parfitt: None. **S.J. Donovan:** None.

Poster

PSTR123: Drug Discovery for Reversing the Effects of Stress

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR123.13/F7

Topic: G.05. Mood Disorders

Support: Swedish Research Council
Karolinska Institutet
AFA
Swedish Brain Foundation
NARSA
Bristol-Meyers-Squibb Unrestricted Neuroscience Grant
European Union (New Mood)

Title: Transcriptomic landscape of five neuropeptides across various regions of the adult human brain using bulk RNA sequencing

Authors: *S. BARDE[1], N. MITSIOS[2], W. ZHONG[3], M. PALKOVITS[4], J. MULDER[5], T. G. HOKFELT[6];
[1]Karolinska Institutet, Stockholm, Sweden; [2]Neurosci., Karolinska Institutet, Solna, Sweden; [3]Sci. for Life Lab., Stockholm, Sweden; [4]Semmelweis Univ., Budapest, Hungary; [5]Dept. of Neurosci., Karolinska Inst., Solna, Sweden; [6]Neurosci., Karolinska Inst. - Biomedicum, Solna, Sweden

Abstract: Neuropeptides are ancillary messenger molecules that co-exist in nerve cells with one or more classic neurotransmitters. They are the most diverse class of signaling molecules in the brain and are engaged in various physiological functions. They act both as transmitters and trophic factors and are implicated in several disorders especially when the nervous system is challenged. In this study, we aim to explore and understand the transcriptomic landscape of neuropeptides in various regions of the human brain. We use in-house generated RNA sequencing data for 967 samples from 202 microdissected regions using the Human Protein Atlas (HPA; *https://www.proteinatlas.org/)*. HPA is a public online database that offers a cohesive overview of transcript and protein expression and distribution in all major human tissue types, including the brain. The microdissected regions include samples from cerebral cortex, hippocampal formation, amygdala, basal ganglia, thalamic and hypothalamic nuclei, midbrain, cerebellum, pons, medulla oblongata and spinal cord. We analyzed data for five neuropeptides of interest i.e. galanin (GAL), somatostatin (SST), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) and secretin (SCT) across all the above-mentioned regions to understand the expression profile for each. GAL was most abundantly expressed (measured as normalized TPM values: nTPM) in the hypothalamus (nTPM: ~1400) followed by medulla oblongata (~107), pons (~30) and thalamus (~23). SST was highly expressed in the hypothalamus (~999) and was also observed in all the other subregions (in between ~33 to ~300). For VIP, the highest expression was seen in the midbrain (~78), hypothalamus (~50) with low expression in the other regions (<20). NPY was highly expressed in the hypothalamus (~880) followed by basal ganglia (~99) and cerebral cortex (~45). The average expression values for secretin across all the subregions were below 20. These results suggest heterogeneity in the expression pattern of the five neuropeptides in the human brain and provides unique transcriptomic signatures for the markers studied. This expression landscape is especially valuable and of importance when exploring the potential of neuropeptide receptors as targets for drug development.

Disclosures: S. Barde: None. **N. Mitsios:** None. **W. Zhong:** None. **M. Palkovits:** None. **J. Mulder:** None. **T.G. Hokfelt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owns stock in H. Lundbeck A/S and BioArctic.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.01/F8

Topic: F.04. Neuroimmunology and Neurovirology

Support: NIH R01HD109095
The Robert & Janice McNair Foundation, McNair Medical Institute
Brain & Behavior Research Foundation NARSAD 28298
Gulf Coast Center for Precision Environmental Health NIH P30ES030285

Title: Opportunistic pathogen increased by maternal Western diet causally contributes to cognitive and metabolic dysfunction in offspring which is resolved by antenatal metformin

Authors: *L. MATZ[1], R. FULTZ[3], C. DI GESU[1], I. BOLDING[1], S. A. BUFFINGTON[2,1]; [1]Ctr. for Precision Envrn. Hlth., [2]Neurosci., Baylor Col. of Med., Houston, TX; [3]GeneDx, Stamford, CT

Abstract: Prepregnancy obesity affects over one million pregnancies per year in the US. Despite the prevalence of prepregnancy obesity and mounting evidence of its adverse effects on offspring health, the underlying mechanisms remain poorly understood and interventions limited. Diet is a primary driver of obesity. We and others have shown that a Western diet (WD), rich in fat but poor in soluble fiber, causes dysbiosis of the gut microbiome in preclinical animal models for diet-induced obesity, consistent with observations in humans. While maternal gut microbiota are emerging as powerful regulators of fetal brain development and metabolism, the effects of WD-induced dysbiosis of the maternal gut microbiome on long-term cognitive and metabolic health outcomes in offspring remain unknown. Here, we hypothesized that (1) maternal WD-induced dysbiosis creates a permissive environment for growth of opportunistic pathogens that are causally related to neurocognitive and metabolic dysfunction in offspring and (2) antenatal targeting of the maternal gut microbiome would improve brain development and cognitive outcomes in affected offspring. We thus assessed cognitive function in offspring born to WD-fed females (MWD) compared with maternal regular diet (MRD) controls and found that MWD offspring underperformed in the hippocampus-dependent contextual fear conditioning paradigm. Given that maternal obesity predisposes offspring to metabolic syndrome, we also assessed total body weight and glucose tolerance at 8 and 20 weeks of age and observed impaired glucose tolerance in MWD offspring relative to MRD controls. Using metagenomic whole genome shotgun (WGS) sequencing, we discovered increased abundance of opportunistic pathogenic bacteria among WD offspring gut microbiota. To fulfill Koch's postulates, we performed daily dosing of conventionally colonized MRD offspring beginning at weaning with one of the opportunistic pathogens identified in the WGS screen and found that it was sufficient to induce MWD offspring-like memory deficits and long-term glucose intolerance, which was reversed by maternal treatment with the antidiabetic metformin. To identify the mechanism by which MWD-associated opportunistic pathogenic bacteria impair host cognitive and metabolic function, we interrogated the offspring serum metabolome and identified a 28% increase in circulating branched chain amino acids in MWD offspring serum compared to that of MRD offspring. Our findings suggest that therapeutic targeting of the maternal gut microbiome throughout pregnancy and lactation is a potential preventative strategy for improving long-term health outcomes in offspring.

Disclosures: L. 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. **C. 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. **I. Bolding:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I.J.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

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.02/F9

Topic: F.04. Neuroimmunology and Neurovirology

Support: The Robert & Janice McNair Foundation, McNair Medical Institute
The University of Texas Medical Branch Institute for Human Infections & Immunity
The University of Texas Medical Branch Sealy Institute for Vaccine Sciences
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Title: In utero exposure to maternal Trypanosoma cruzi infection alters cortical development, drives dysregulated risk assessment and social dysfunction in offspring

Authors: L. E. RIOS[1], K. A. BUCHANAN[2], L. M. MATZ[3], I. J. BOLDING[3], I.-C. WANG[4], N. J. GARG[5], ***S. A. BUFFINGTON**[6,7];
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Abstract: Maternal immune activation (MIA) during pregnancy increases risk for neurodevelopmental disorders in offspring. The effects of maternal parasitic infection on offspring neurodevelopment, however, remain almost completely unexplored. Chagas disease is a prevalent neglected tropical disease caused by the vector-borne parasite *Trypanosoma cruzi* (*Tc*). Acute *Tc* infection results in immune activation characterized by the induction of proinflammatory cytokines, including IL-6 and IL-17A, which play a complex role in host defense *versus* pathogenesis. Pathological activation of the IL-17A pathway is a mediator of neurodevelopmental impairment in the MIA model for autism spectrum disorder (ASD). MIA disrupts cortical lamination, perturbs network connectivity, and increases neuroinflammation - pathology associated with ASD-like behavioral deficits in offspring. Unfortunately, frontline

anti-parasitic drugs are contraindicated during pregnancy, leaving pregnant women little recourse for protecting their developing child/ren from inflammatory sequalae resulting from *Tc* infection. Given that the maternal proinflammatory response to *Tc* infection serves as a protective mechanism against neonatal infection but simultaneously leads to potentially pathogenic levels of circulating IL-6 and IL-17A, we hypothesized that *in utero* exposure to maternal *Tc* infection would adversely affect offspring neurodevelopment and behavioral outcomes irrespective of congenital transmission. Here, we report that periconceptional *Tc* infection drives expansion of the T helper 17 cell (Th17) population while decreasing regulatory T cells (Tregs) in dams. Male and female *Tc* offspring demonstrate dysregulated risk assessment, characterized by excessive risk tolerance, and anomalous social behavior. Analysis of cell type-specific and activity-dependent markers in the offspring brain and metagenomic sequencing of the maternal and offspring gut microbiome reveal mechanisms by which *in utero* exposure to maternal *Tc* infection alters offspring brain development, function, and behavior. Our data suggest prioritizing vaccination against *Tc* for women of childbearing age living within the habitable zone of triatomines - the primary *Tc* vector - could reduce risk for adverse neurodevelopmental outcomes in children.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Program #/Poster #: PSTR124.03/F10

Topic: F.04. Neuroimmunology and Neurovirology

Support: Wellcome Trust IMAT
The Francis Crick Core funding

Title: Modeling Autoimmune Psychosis in Mice via NMDAR Immunization: Behavioral and Immunological Insights

Authors: *L. HE, T. NGUYEN, H. FELDMAN, K. SCHMACK;
The Francis Crick Inst., London, United Kingdom

Abstract: Objective: Psychotic diseases such as schizophrenia are associated with immune alterations. Recent clinical evidence suggests a correlation between psychosis and autoimmunity, which has led to the proposed disease category of 'autoimmune psychosis.' However, the underlying mechanisms are not well understood. This study aims to develop a murine model of autoimmune psychosis through NMDAR immunization to explore how autoimmune responses give rise to behavioral abnormalities characteristic of psychosis.**Methods:** Mice were immunized with NMDAR mRNA-lipid nanoparticles. Behavioral assessments were conducted using prepulse inhibition tests, digital ventilated cages, Motion Sequencing (MoSeq), to monitor

psychosis-like behaviors,locomotion, seizure activity, and other signs. The progression of autoimmunity and inflammation was closely monitored using ELISA, flow cytometry and immunohistochemistry on various organs.**Results:** Preliminary findings show that all immunized mice exhibited abnormal behaviors post-immunization. Specifically, 50% of the mice displayed hyperlocomotion, 25% suffered episodic seizures, and 12.5% developed a persistent head tilt. Although no overt brain inflammation was observed, significant meningeal inflammation was identified. Ongoing analyses are focusing on detailed characterization of the behavioral phenotypes and the immunophenotypes of these mice.**Conclusion:** Our model indicates a link between NMDAR autoimmunity and the emergence of specific behavioral syndromes in mice. The significant meningeal inflammation, absent or mild corresponding brain inflammation, prompts further exploration into how distant meningeal immune responses affect brain neural pathways. These findings may lead to new therapeutic targets for treating autoimmune psychosis.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Program #/Poster #: PSTR124.04/F11

Topic: F.04. Neuroimmunology and Neurovirology

Support: DGAPA-PAPIIT UNAM IA-207321

Title: Activation of GFAP cells in cerebellum induced by high-fat diet in a model of metabolic syndrome

Authors: D. LEÓN AGUILAR[1], ***L. UBALDO**[2], E. ESPITIA[3], R. NORIEGA[4], L. NAVARRO[5];
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Abstract: Obesity induced by a high-fat diet causes metabolic alterations; when describing diets, the effects on weight, adiposity, and glucose are usually included. However, controversy exists over the neuroinflammation that is triggered by a fatty diet in short periods. This study aims to analyze morphological changes and behavioral tests of a diet enriched with olive oil and lard over metabolism by employing an experimental rodent model. Adult male Wistar rats were randomly assigned to one of two conditions: a normal fat diet (NFD) fed with chow or a high-fat diet group (HFD). Both groups' weight gain and food consumption were quantified weekly throughout the experimental period. After eight weeks of diet, *ex vivo* analyses were performed. Rats fed with a high-fat diet gained more weight compared to the NFD group; additionally, they accumulated significantly more epididymal, subcutaneous, and retroperitoneal fat. Food intake followed inverse patterns of body weight gain, where food intake was lower in rats fed with the

high-fat diet than in those fed with the control diet. In addition, the HFD group displayed metabolic syndrome including glucose homeostasis and insulin sensitivity; moreover, this group showed increased adipokine secretion. In the cerebellum was found more activity of GFAP cells and this correlated with change in response motor coordination using a special rota-rod. This study shows that a short-term fat-enriched diet based on lard and olive oil causes the activation of glial cells and has negative effects on functional actions.

Disclosures: D. León Aguilar: None. **L. Ubaldo:** None. **E. Espitia:** None. **R. Noriega:** None. **L. Navarro:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Support: Horizon 2020 ITN-European Training Network SmartAge (859890)
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Title: Antibiotic-mediated peptidoglycan release alters synaptic gene expression and social behavior in mice

Authors: *I. MARTÍNEZ SÁNCHEZ, C. HEATHER, S. NYLÉN, R. DIAZ HEIJTZ; Karolinska Institutet, Stockholm, Sweden

Abstract: A rapidly expanding body of research has identified the gut microbiota as a key regulator of brain development, function, and behavior. Concurrently, there is growing concern that commonly used broad-spectrum antibiotics (ABX), which reduce microbiota diversity, could have detrimental effects on the central nervous system, thereby contributing to the neurobiology of human brain disorders. Recent studies have shown that β-lactam ABX such as ampicillin increase the release of bacterial peptidoglycans (PGN) from the gut microbiota into the periphery (Tan et al., 2021). Here, we tested the hypothesis that ABX treatment can also lead to a PGN brainstorm, resulting in neuroinflammation and behavioral changes. For this purpose, we exposed 8-week-old C57BL/6 male mice (n=12) to ABX (ampicillin; 1 mg/ml) in their drinking water and analyzed PGN levels in serum and brain at different time points (24h, 48h, 72h and 1 week). Our results showed that ABX treatment transiently increases PGN levels in both serum and brain, in a region-specific manner. Moreover, ABX-treated mice displayed decreased sociability and social cognition in the three-chambered social approach task. These behavioral changes were associated with reduced gene expression of synaptic-related markers, including synaptophysin and PSD-95, and altered expression of two putative PGN transporters (SLC15a4 and SLC46a3) in the prefrontal cortex, a crucial region for social and emotional behaviors. Furthermore, decreased expression of various tight junction proteins, critical for gut barrier

integrity, was observed in the colon. These novel insights suggest that repeated ABX therapy may adversely affect synaptic functions by transiently elevating PGN levels in the brain.

Disclosures: I. Martínez Sánchez: None. **C. Heather:** None. **S. Nylén:** None. **R. Diaz Heijtz:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Topic: F.04. Neuroimmunology and Neurovirology

Support: 5R01NS112399-05
5R00NS114107-04
HHMI Hanna H. Gray Fellowship
Harvard Tan-Yang Center for Autism Research

Title: Immunologic control of social behavior

Authors: *Z. SULLIVAN[1], J. OSTERHOUT[2], V. KAPOOR[1], S. CRAIG[1], C. G. DULAC[1]; [1]Harvard Univ., Cambridge, MA; [2]Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: Host defense systems are essential for survival and ubiquitous across the tree of life. In animals, defense involves both antimicrobial activity and sickness, in which neuroimmune interactions generate physiological and behavioral changes such as fever, anorexia, and social withdrawal during infection. We previously identified a population of hypothalamic neurons that control fever and appetite during sickness. However, the cellular and molecular mechanisms that modify social behavior during sickness remain poorly understood. To study this, we modeled bacterial infection in mice via injection of lipopolysaccharide (LPS) to generate an acute sickness state.

As expected, sick animals interacting with healthy animals exhibited antisocial behavior. Strikingly, we found that interactions between LPS-injected animals were prosocial, characterized by huddling behavior between sick conspecifics. This illustrates that sickness behaviors are modulated by environmental context. We found that prosocial behavior between LPS-injected animals was controlled by prostaglandin signaling to oxytocinergic neurons in the paraventricular nucleus of the hypothalamus (PVN), which establishes a node for neuroimmune control of social behavior during sickness. In surveying downstream areas that may control this behavior, we identified oxytocin receptor-expressing neurons in the paraventricular thalamus (PVT) that are specifically active during sickness-induced social avoidance. Genetic and functional manipulation of this population demonstrated that it controls context-dependent social behavior during sickness. Importantly, these results demonstrate that both appetitive and aversive social interactions can be driven by oxytocin.

In summary, we identified a novel sickness behavior revealed by surveying sickness across

social contexts. We defined a neural circuit mechanism by which the inflammatory signals modulate the activity of oxytocinergic neurons to give rise to context-dependent sickness behaviors, and identified both pro- and antisocial roles for oxytocin. Our studies point to a direct link between the immune system and neural control of social interaction, thereby establishing a mechanism for changes in social behavior during sickness.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Program #/Poster #: PSTR124.07/F13

Topic: F.04. Neuroimmunology and Neurovirology

Support: 5 R01 AI178725-02

Title: The Key to Lyme: Murine Modeling of Acute Lyme Disease Neurological Symptoms

Authors: *K. MYKYTEN[1], P. GWYNNE[2], L. HU[2], C. G. DULLA[1];
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Abstract: Lyme Disease (LD) is caused by infection with *B. burgdorferi*, the incidence of which has nearly doubled in the U.S. since 1990. It is characterized by symptoms including fever, headache, and musculoskeletal pain. If infection goes untreated, more severe conditions such as facial palsy and peripheral neuropathies can develop. LD patients are also at risk of developing Post Treatment Lyme Disease Syndrome (PTLDS), characterized by peripheral neuropathies, fatigue, and cognitive difficulties. Our long-term goal is to understand the mechanisms that drive neurological dysfunction, inflammation, and pain-phenotypes in LD and PTLDS. Here we present our initial experiments developing murine neurological behavioral testing of behavioral, cognitive, and sensory dysfunction in LD, which we will then expand to PTLDS. Our goal is to better understand LD neuropathology and potential pathways for the development of PTLDS. Male and female 7-8 week-old C3H/HeN mice were tested using a series of behavioral tests related to LD associated symptoms. Mice were infected with 10^4 *B. burgdorferi* via subcutaneous injection. Control mice were injected with an equivalent volume of saline solution. Researchers doing behavioral testing were blinded to the infection condition. Beginning with a baseline measurement before *B. burgdorfer*i infection, mice underwent behavioral testing at 2, 4, 6, and 8 weeks after infection. Behavioral tests included the Von Frey Test, Cold Plate Test, Open Field Testing, Classical Light/Dark Avoidance Assay, Light/Dark Photosensitivity Assay, Y-Maze Test, and Grip Strength Test. Mice were weighed biweekly to track general body condition. To minimize confounds between tests, each cohort of mice underwent a maximum of three different tests during the timeline and no more than one nociceptive test per day. Preliminary data suggests acutely infected LD mice show significant differences (n=4,4: two-

sample t-test, p<.001) at 4 weeks of infection compared to controls in the Grip Test. Four-week infected mice also show a trend of decreased alternation on the Y-Maze Test, decreased motor activity during the Classical Light/Dark Avoidance Assay (n=4,4), and decreased (n=3 ,1) latency to nociceptive behavior in the Cold Plate Test. Possible differences are shown at 4 weeks during the Von Frey Assay (n=2,1), but more data is needed for all tests. This suggests that LD symptoms can be translated to a mouse model, specifically increases in musculoskeletal pain as well as potential increases in lethargy, cognitive function, allodynia, and mechanosensitivity.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Topic: F.04. Neuroimmunology and Neurovirology

Support: GW4 BioMed MRC Doctoral Training Partnership
Future Leaders in Neuroscience Research, Cardiff University

Title: Regulatory T-cell depletion affects anxiety-like behaviours in mice.

Authors: *F. R. SHEPHERD[1], T. HUMBY[2], N. CLIFTON[3], E. STERGIAKOULI[4], J. HALL[1], M. CLEMENT[1], L. S. WILKINSON[5], W. DAVIES[6];
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Abstract: Regulatory T cells (Treg) are key homeostatic mediators of the immune system with vital roles in regulating innate and adaptive immune forces. Tregs prevent autoimmunity and oversee neuroimmune interactions between astrocytes and microglia. Lower circulating Treg levels and activity have been observed in multiple mood-psychotic spectrum conditions including depression, anxiety and schizophrenia. In transgenic mice expressing the diphtheria toxin (DT) receptor in FoxP3^{+} cells only, DT administration results in acute and specific Treg depletion. This model can be used to assess downstream consequences of Treg-depletion on neurobiological and behavioural measures of relevance to mood and psychotic disorders. The behaviour of Treg-depleted (DT administered 15μg/kg i.p. twice, two days apart) and non-depleted (vehicle administered) female and male FoxP3-DTR (diphtheria toxin receptor) C57BL/6J mice was compared (Treg depleted group n= 22 (12 female, 11 male); vehicle group n= 19 (9 female, 10 male)), aged 85-100 days old). Mice were tested across a range of behavioural assays taxing symptom domains related to mood-psychosis spectrum conditions: elevated plus maze, open field, spontaneous alternation, sucrose preference, rotarod and startle with pre-pulse inhibition tests. To confirm Treg depletion, *post mortem*, fresh spleens were

weighed and prepared for flowcytometry analysis; cell surface and intracellular staining were performed with monoclonal antibodies against CD3, CD4, and FoxP3.As expected, there was a significant decrease in $CD4^{+}FoxP3^{+}$ cells in splenocytes of the Treg depleted group following the DT injection schedule. Treg-depleted mice showed no evidence of gross adverse effects on health, and performed equivalently to control mice in most behavioural tests. However, there was a significant, and sex-specific, effect on elevated plus maze open arm time (controlling for activity), with female Treg depleted mice spending less time in this portion of the maze than male Treg depleted, and control, mice. These findings show that using the 2-dose DT injection schedule, peripheral Tregs can be largely eliminated without causing sickness behaviour. They suggest an activity-independent effect of Treg depletion on anxiety-related measures in female subjects. Further work will test a) whether this behavioural effect generalizes to other anxiety measures, and b) the extent to which it is due to central or peripheral Treg depletion and the imbalance between central and/or peripheral pro- and anti-inflammatory factors. These studies will have relevance for understanding the role of immune factors in vulnerability to psychiatric conditions.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Program #/Poster #: PSTR124.09/F15

Topic: F.04. Neuroimmunology and Neurovirology

Support: NIDA/NIH

Title: Ccl2 antagonist rs504393 reverses heroin-induced hyperalgesia and place aversion in adult male and female rats

Authors: *N. SAID;
NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD

Abstract: Over the last two decades, opioid overdose has become the leading cause of accidental deaths in the United States, causing nearly 500,000 deaths from 1999 to 2019. Recent evidence suggests that glial activation and the related neuroimmune signals may be involved in the dependence-inducing properties of opioids. Methadone, buprenorphine, and naltrexone are currently used as treatments for opioid use disorder (OUD), whereas naloxone is used in cases of opioid overdose. Although these treatments have proven effective, relapse rates remain high. Therefore, the identification of non-opioid, new targets for the treatment of OUD is urgently needed. The main purpose of this study is to investigate the potential of a novel neuroimmune marker CCL2/MCP-1 in opioid withdrawal-related behavior in rats. Our hypothesis is that CCL2 is involved in behaviors associated with heroin withdrawal like hyperalgesia or hyperkatifeia

(emergence of negative emotional states). To that end, we chose to work with a potent CCL2 antagonist, RS504393. We first measured whether it could affect hyperalgesia using the von Frey and Hargreaves tests, for mechanical and thermal sensitivity, respectively, after two weeks of repeated heroin subcutaneous administration in adult male (*n*=22) and female (*n*=23) Wistar rats. We also investigated its impact on the heroin withdrawal-induced conditioned place aversion (CPA) and naloxone-precipitated somatic withdrawal. Additionally, we assessed the effect of RS504393 on anxiety using the novelty suppressed feeding test and anhedonia via the sucrose preference test in adult rats undergoing heroin withdrawal. Results showed that mechanical and thermal hyperalgesia were significantly reversed by the CCL2 antagonist in both males and females. Moreover, it attenuated CPA and somatic withdrawal symptoms compared to nondependent rats. However, no significant effect of RS504393 were observed on anhedonia, or on anxiety-like behavior. Overall, these findings highlight the therapeutic potential of CCL2 antagonism in mitigating opioid-induced hyperalgesia and negative affective states, underscoring its relevance as a promising pharmacological target for opioid addiction treatment. Further investigations are warranted to elucidate the underlying mechanisms and establish CCL2 antagonist RS504393 as a potential treatment for OUD.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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Title: Cell specific effects of TLR9 knockout and contextual fear conditioning on hippocampal gene expression

Authors: *E. WOOD[1], A. CICVARIC[2], V. JOVASEVIC[3], H. ZHANG[2], Z. PETROVIC[4], A. CARBONCINO[5], K. PARKER[6], T. E. BASSETT[7], N. YAMAWAKI[8], H. LOGIN[9], F. SANANBENESI[10], A. FISCHER[11], J. M. RADULOVIC[12];
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Med., The Bronx, NY; [8]Aarhus Univ., Aarhus, Denmark; [9]Biomedicine, Aarhus Univ., Aarhus C, Denmark; [10]ENI, Göttingen, Germany; [11]German Ctr. For Neurodegenerative Dis., Goettingen, Germany; [12]Neurosci., Albert Einstein Col. of Med., New Rochelle, NY

Abstract: While early changes to gene expression from 1 to 24 hours following learning are well characterized, genetic changes occurring at later time points are less well known. In our previously published work, we made the exciting discovery that inflammatory gene expression, especially that of toll-like receptor 9 (TLR9), increases 96 h after learning via bulk-RNA sequencing. We then performed single nucleus RNA sequencing (snRNA-seq) of naïve, home cage control mice or of mice 96 hours after contextual fear learning (CFC), with both control and TLR knockout (KO) mice, to determine the cell specific effects of CFC and TLR9 KO. Our analyses identified 29 clusters and robust (greater than 1.5-fold) differential expression of 144 genes by CFC and 396 for TLR9 KO. Across clusters, *ATPv0c* and *Hsp90b1*, genes essential for TLR9 function, were consistently upregulated by CFC at this delayed timepoint. Furthermore, we identified numerous doublecortin-positive (DCX^+) neurons, not just of dentate gyrus clusters, which lost their DCX^+ phenotype following CFC. This, along with CFC induced fluctuations of *vGlut2*, demonstrated dramatic phenotypic fluctuations during memory formation. Within DCX^- excitatory neurons of the CA1, reactome pathway analysis revealed significantly increased pathways associated with memory formation, including vesicle mediated transport, membrane trafficking, protein and RNA metabolism, and transcription, but also those less intuitively associated to memory including cell cycle, immune system, and DNA repair. Interestingly, TLR9 KO blocks CFC induced gene expression changes, inducing completely opposite trends in transcript regulation, without affecting these genes relative to the naïve control group, apart from one small cluster which underwent CFC unrelated changes. This study reveals widespread, ongoing changes in gene expression four days after CFC, with those of increased expression blunted by Tlr9 KO. The results highlight more extensive phenotypic changes and identify mechanisms by which disruption to TLR9 mediated inflammatory signaling may impair memory formation.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

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

Support: Grant PROSNII-UdeG 2024 To GCH
Grant CUAltos-UdeG To GCH

Title: Does Lupinus Exaltatus Zucc Extract modulate the expression of HSP-16.2 in C. elegans?

Authors: *G. CAMARGO HERNÁNDEZ[1], L. A. RAMIREZ CONTRERAS[2], D. W. AGUILAR OCAMPO[3], S. A. GUTIERREZ-RUBIO[4], A. CASTILLO-ROMERO[3], L. A. HERNÁNDEZ VILLASEÑOR[5], M. S. REVELES GONZÁLEZ[6], M. MACÍAS-CARBALLO[11], L. M. ANAYA ESPARZA[7], J. ACEVES ARIAS[8], S. SANCHEZ[9], L. HERNANDEZ[10]; [1]CUAltos UNIVERSIDAD DE GUADALAJARA, Guadalajara, Mexico; [2]Univ. de Guadalajara, Tepatitlán de Morelos, Mexico; [4]Dept. de Fisiologia, [3]Univ. de Guadalajara, Guadalajara, Mexico; [5]Univ. de Guadalajara, La Barca, Mexico; [6]Univ. de Guadalajara, Tepatitlan de Morelos, Mexico; [7]Ciencias Pecuarias y AgrIcolas, Univ. de Guadalajara, Tepatitlán, Mexico; [8]Univ. de Guadalajara, Atotonilco el Alto, Mexico; [9]Clinicas, Univ. de Guadalajara, Tepatitlan de Morelos, Mexico; [10]Fisiología, Univ. de Guadalajara, Guadalajara, Mexico; [11]Dept. de clínicas, CUAltos Univ. de Guadalajara, Tepatitlán de Morelos Jalisco, Mexico

Abstract: The genus *Lupinus L.* (Fabaceae) with complex taxonomy It has more than 200 species, most of them distributed in America, with 13 species in the region of the Mediterranean and 2 in tropical Africa (Lewis et al., 2005). They occupy habitats such as alpine grasslands and moors, It predominates at altitudes above 3000 meters. (Hughes and Eastwood, 2006). In Mexico, more than 100 species of *Lupinus* (Bermúdez-Torres et al., 2002), which are distributed widely in temperate and cold zones and sometimes in regions very wet or dry. Various studies in our country have been aimed at characterizing the nutritional composition and phytochemistry of this genus. These studies highlight Zamora-Natera y Terrazas. - Leaf and petiole anatomy of Lupinus the importance of these species due to their content of secondary metabolites, mainly flavonoids and quinolizidine alkaloids, which have been the subject of study for its pharmacological and agricultural applications (García et al., 2004; Przybylak et al., 2005). **AIM:** To evaluate the effect of *EMLE* against oxidative damage induced on the model organism *C. elegans*. **MATERIAL AND METHODS**: We used adult *C. elegans* N2 Wild Type strain, and the transgenic strain TJ375. In N2 nematodes, survival at different doses of *EMLE* was measured, and the effect of Heat Shock (HS) at 34°C for 1h on the expression of HSP-16.2 Chaperone was examined in TJ375::GFP in Groups: Control, HS, EMLE and EMLE+HS. **RESULTS**: EMLE had no effect on the survival. In nematodes TJ375 exposed to HS increased the expression of HSP-16.2 was observed *VS* Control group. While treatment with *EMLE* (0.5 mg/mL) during HS decreased the expression of HSP-16.2::GFP with respect to the Control group. However, without HS We observed an increase in the expression of HSP-16.2::GFP protein. **CONCLUSIONS:** Our results suggest that probably EMLE induces protection by increasing the expression of proteins in response to Stress. Furthermore, the ability of EMLE could modulate the expression of some fundamental genes in the Insulin/IGF-1 signaling pathway (IIS), involved in longevity and oxidative or heat shock Stress response.

Disclosures: G. Camargo Hernández: None. **L.A. Ramirez Contreras:** None. **D.W. Aguilar Ocampo:** None. **S.A. Gutierrez-Rubio:** None. **A. Castillo-Romero:** None. **L.A. Hernández Villaseñor:** None. **M.S. Reveles González:** None. **M. Macías-Carballo:** None. **L.M. Anaya Esparza:** None. **J. Aceves Arias:** None. **S. Sanchez:** None. **L. Hernandez:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.12/F18

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

Title: Elucidating the role of ATF3 in the neuropathology of a mouse model of Leigh Syndrome

Authors: *M. BLANCO-RAMOS[1], P. PRADA-DACASA[1], C. JIMÉNEZ FLÓREZ[1], A. DOMINGUEZ[1], A. GELLA[2], E. SANZ[3], A. QUINTANA[4];
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Abstract: Mitochondrial energy-generating machinery mutations cause mitochondrial disease (MD), a diverse group of orphan neuromyopathies. Leigh Syndrome is the most common pediatric MD, leading to severe encephalopathy and premature death. Albeit clinically heterogenous, LS is characterized by progressive neuronal damage, which is anatomically restricted to brainstem and basal ganglia, revealing that not all neurons are equally susceptible to mithocondrial dysfunction.We have previously demonstrated that GABAergic and glutamatergic neurons are vulnerable to the disease in mice lacking the Ndufs4 subunit (Ndufs4KO), a well-characterized model of LS that recapitulates the human disease. However, the underlying mechanisms leading to neuronal demise remain unknown, underscoring the need to develop novel treatments, as it remains an incurable pathology. To dissect the mechanisms affected in glutamatergic neurons, we combined mouse genetics which cell-type specific transcriptomics. RnaSeq results showed an upregulation of the activating transcription factor 3 (*Atf3*) in glutamatergic neurons in the vestibular nuclei of Ndufs4KO, an area severely affected by the disease. Remarkably, induction of this transcription factor is also observed in brains from Leigh Syndrome patients, suggesting that this is a conserved response to mitochondrial dysfunction.To dissect the contribution of ATF3 to the pathology, we generated and characterized a Ndufs4KO mouse line lacking ATF3. Our results show that deletion of *Atf3* rescues synaptic loss and attenuates microglial reactivity in glutamatergic brain regions of Ndufs4KO mice, coincident with a partial restoration of breathing impairments without any effect on lifespan.Overall, our results highlight a role for ATF3 in the development of microglial reactivity and neuronal synaptic loss in the context of mitochondrial dysfunction. These results offer a potential therapeutic approach for the neurodegenerative processes underlying MD.

Disclosures: M. Blanco-Ramos: None. **P. Prada-Dacasa:** None. **C. Jiménez Flórez:** None. **A. Dominguez:** None. **A. Gella:** None. **E. Sanz:** None. **A. Quintana:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.13/F19

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

Title: Investigating the Elevated Gene Expression in Simultaneous Malignant Brain Tumors and Multiple Sclerosis: Significance for Understanding the Underlying Mechanisms and Possible Drugs Targets.

Authors: J. H. VELASCO, Jr.[1], *L. ÁLVAREZ-PALAZUELOS[2], A. RUIZ RAMIREZ[1]; [1]Res. Dept., Univ. Autonoma de Guadalajara, Guadalajara, Mexico; [2]Univ. De Guadalajara, Guadalajara, Mexico

Abstract: Concurrent gliomas and multiple sclerosis present a challenging clinical scenario, demanding a thorough understanding of their molecular underpinnings. Our research aimed to decipher the intricate interplay between neuroimmunological factors and tumor biology by investigating gene expression profiles. This approach sheds light on potential shared pathways contributing to the development and progression of both conditions. Using data from pre-existing literature that conducted an array-based methylation profiling on a cohort of 26 patients diagnosed with primary brain tumors and co-occurrence of multiple sclerosis, we analyze the RNA-seq data from the GEO database with the ID GSE243465. With the use of GEO2R, we analyzed various chromosome regions that identified 68 genes in total. Expression analysis revealed several upregulated genes on chromosome 1, including PEX10, MYOM3, GABP2, and PERM1. PEX10, an E3 ubiquitin-protein ligase component, has been implicated in functions like import of normal matrix and biogenesis of peroxisome; in MS patients, a reduced peroxisomal transcript and protein levels have been recognized in recent years. MYOM3's association with muscle structure hints at its relevance to muscular dystrophies. GABP2's role as a transcription factor suggests regulatory functions in neuroimmunological processes and normal lymphocytes development. PERM1's has been involved in glucose and lipid metabolism and immune pathways. These findings provide valuable insights into the molecular mechanisms underlying concurrent gliomas and multiple sclerosis, offering potential targets for further investigation and therapeutic intervention. They underscore the importance of exploring shared molecular pathways between neuroimmunological disorders and cancer, advancing our understanding and informing future treatment strategies. This research has broader implications for elucidating the complex etiology of these conditions and may pave the way for personalized approaches to diagnosis and therapy.

Disclosures: J.H. Velasco: None. **L. Álvarez-Palazuelos:** None. **A. Ruiz Ramirez:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.14/F20

Topic: B.09. Glial Mechanisms

Title: Optimization of anesthesia and microwave fixation conditions for biochemical and morphological studies of glycogen metabolism after behavioral tests

Authors: *M. F. VELOZ CASTILLO[1,2,3], C. CALI[4,3], P. J. MAGISTRETTI[1];
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Abstract: Glycogen is the largest cerebral energy reservoir and is localized in astrocytes under normal physiological conditions. Astrocytes possess the enzymatic machinery necessary for glycogen breakdown and its further conversion to lactate, which can be shuttled to neurons via monocarboxylate transporters to fuel their tricarboxylic acid cycle (a mechanism known as Astrocyte-Neuron Lactate shuttle, or ANLS). Therefore, one of the primary roles of glycogen is to provide a metabolic buffer during neurotransmission. The role of glycogen metabolism in long-term memory formation, learning-dependent synaptic stabilization, memory consolidation, and maintenance of long-term potentiation has been previously demonstrated (Suzuki, et al. 2011; Scavuzzo, et al. 2021). Nonetheless, accurately quantifying brain glycogen levels at different stages of the memory consolidation process is still a challenge. In the present work, we use a microwave fixation system as euthanasia and fixation method to preserve glycogen levels in a way that reflects as much as possible *in vivo* conditions by halting enzymatic activity by instantaneous heat induction. We compare the effects of six different anesthetic protocols and three microwave fixation settings to determine the adequate condition for glycogen quantification. Our results show clear sex-specific differential effect depending on the anesthetic used on brain glycogen concentration. Furthermore, using volume electron microscopy, we have identified optimal microwave fixation conditions that yield an acceptable preservation of morphology. Our results provide evidence for optimal anesthetic and microwave fixation protocols to study glycogen metabolism after behavioral paradigms.

Disclosures: M.F. Veloz Castillo: None. **C. Cali:** None. **P.J. Magistretti:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.15/F22

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

Title: Deciphering the role of lactylation in a mouse model of Leigh Syndrome

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(Barcelona), Spain; [2]Institut de Neurociències, Universitat Autònoma de Barcelona (UAB), Bellaterra (Barcelona), Spain

Abstract: Primary mitochondrial diseases (MD) are a group of progressive neurodegenerative disorders caused by alterations in the mitochondrial machinery involved in energy generation, affecting high energy-demanding tissues such as the brain. Neurological damage plays a pivotal role in MD pathology, in which some neuronal populations are more susceptible to be affected by the progression of the disease. However, the underlying mechanisms participating in the regional and cellular specificity remain elusive. Growing evidence suggests that lactate, an end-product of glycolysis increased in a context of mitochondrial dysfunction, not only acts as a metabolic fuel, but also serves as a donor for lactylation, a post-translational modification that regulates gene expression and cellular functions. Using a mouse line lacking mitochondrial complex I subunit NDUFS4 (a model of Leigh Syndrome (LS); Ndufs4KO), we have studied the interplay between the addition of lactyl moieties to non-histone and histone proteins, and cellular damage. Our results show that protein pan-lactylation and histone H3 lactylation are increased at late stages of the disease (P55-60) in the olfactory bulb (OB), cerebellum (CB) and brainstem (BS), which are key areas for the progression of the disease. Consistent with these findings, lactate levels are also increased in these brain regions, being more prominent in the OB and the BS. In addition, histological assessment in both mice and post-morten brain tissue from MD patients enabled us to define the contribution of lactylation to neuronal damage and glial reactivity. Finally, considering that modulation of lactylation could offer a novel therapeutic approach for MD, the effect of the pharmacological manipulation of lactate transport between astrocytes and neurons, and the production of lactate through inhibition of lactate dehydrogenase (LDH), were also assessed. These results will provide new insights into the pathology of LS.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.16/F23

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

Support: Maine INBRE

Title: The role of aluminum in associative learning in Drosophila

Authors: *G. CRYSTAL NOVI, S. AHMAD;
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Abstract: Aluminum is a common element in people’s daily lives, being used in many everyday products, such as cans, pans, and cooking foil. Aluminum is also a component of products such as deodorants, cosmetics, antiacids, and food additives. Because it is so common, it can be hard to imagine that aluminum exposure could cause any problems. However, according to the Center

for Disease Control and Prevention, although everyone is exposed to low levels of aluminum, exposure to high levels may result in neurological problems. For example, studies in rats suggest that aluminum exposure is associated with oxidative stress, gliosis, loss of neurons, and higher expression of hyperphosphorylated tau and amyloidogenic proteins. *Drosophila* is a well-established model to study neurodegenerative diseases and dementia because of its short lifespan, inexpensive maintenance, and the possibility of genetic manipulation. However, to the best of our knowledge, the effects of aluminum on cognition in flies are not well known. Aluminum's toxicity could be causing neurological problems and even playing an Alzheimerogenic role, so it is important to study its role in cognitive decline. Our work aims to understand the effect of aluminum on cognition in *Drosophila*, starting with disruptions to associative learning.*Drosophila* is already used to model associative learning, so our aim was to adapt a cost and time-effective associative learning assay that could be used as a proxy for cognitive decline. We used quinine as an aversive stimulus to suppress the phototactic tendencies of *Drosophila*; that is, their tendency to go toward light. Flies exposed to aluminum and trained with quinine did not show a significant difference in performance in comparison to flies trained with water. That is, the suppression of phototactic tendencies was reduced, suggesting that aluminum disrupts associative learning. Our goal was to establish how changes in concentration and exposure timeline enhance or reduce the effects of aluminum exposure, as well as to explore possible mechanisms for the disruption.
By establishing the role of aluminum in disrupting at least one cognitive function, we will be able to gain insight into the possible effects of long-term and excessive exposure to aluminum.

Disclosures: G. Crystal Novi: None. **S. Ahmad:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.17/F24

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

Support: UdeG PIN 2021-11 to LH
UdeG ProSNI 2023 to LH

Title: Effect of the Enteropathogenic Escherichia coli infection on GABAergic activity in the model organism Caenorhabditis elegans

Authors: *L. HERNANDEZ[1], D. AGUILAR OCAMPO[2], L. A. RAMIREZ CONTRERAS[3], A. CASTILLO-ROMERO[4], T. A. GARCIA[6], S. A. GUTIERREZ-RUBIO[5], G. CAMARGO HERNÁNDEZ[7];
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Mexico; [6]Fisiologia, Univ. de Guadalara, Zapopan, Mexico; [7]Ciencias de la Salud, CUAltos UNIVERSIDAD DE GUADALAJARA, Guadalajara, Mexico

Abstract: Introduction. Intestinal microbiome disorder and its relationships with normal physiology is collectively called "gut dysbiosis", which has been identified as an important factor leading to diseases, by altering the homeostasis of neurotransmitters. Among these neurotransmitters, the inhibitory GABA (gamma-aminobutyric acid), is involved in pathways and functions of the CNS, such as behavior, motor control, mood, or sleep. Also important is the effect that pathogenic bacteria have on the generation of intestinal dysbiosis. We are interested in infectious diarrhea caused by diarrheagenic Escherichia coli strains, such as the enteropathogenic *E. coli* (EPEC), which is an important cause of childhood morbidity and mortality worldwide, and a common reason for hospital stay and pediatric consultations. Unfortunately, the complexity of the nervous system and the diversity of the intestinal microbiota in mammals hinder the understanding of their interaction. However, this can be investigated in a simpler and more defined model, the nematode *Caenorhabditis elegans*, widely used in studies of microbial pathogenesis and which has a simple nervous system that includes the GABAergic system. Objective: To evaluate the effect of enteropathogenic Escherichia coli infection on GABA activity in Caenorhabditis elegans. Methodology: C. elegans strains N2 Bristol (WT) and EG1653 (oxIs22 [unc-49p::unc-49::GFP + lin-15(+)] X) were used, which were distributed depending on the experiments in a CONTROL group, fed with their standard food, E. coli OP50, and an EPEC group, fed with Enteropathogenic *Escherichia Coli.* The Assays were done on days 1, 2, and 3 of infection. To evaluate changes in the GABAergic system functionality, N2 worms were subjected to the Nose Touch (NoT) Assay. To determine if there were changes in $GABA_A$ receptors, EG1653 worms were mounted on a 2% agarose pad placed on a slide, and immobilized by a drop of 40 mM Sodium Azide; They were subsequently observed in an epifluorescence microscope. Results. The shrinking response in the NoT Assay indicates damage in the GABAergic system. This was recorded with EPEC in 22% of the trials on day 1, decreasing to 6% on day 2 and disappearing on day 3. EG1653 worms infected by EPEC showed a decrease, relative to the control, in $GABA_A$ receptors of 31% and 44% in the dorsal and ventral body area, respectively. Conclusion: The results suggest that EPEC infection decreases GABAergic activity, with a subsequent recovery.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.18/F25

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

Support: NIH U01AI093504: Novel Therapeutic Approaches to Treatment of Botulinum Neurotoxin Poisoning
NIH 1R01AI173059: A versatile structure-based therapeutic platform for development of VHH-based antitoxin and antiviral agents
DTRA Fundamental Research Project CB11178: Treatment of botulism with 3,4-diaminopyridine phosphate

Title: Reversible Chemo-denervation to Study Mechanisms of Atrophy

Authors: *T. G. WENTZ, Z. D. CHANDLER, P. M. MCNUTT;
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Abstract: Muscle atrophy is a clinical morbidity which profoundly impacts quality of life. Rodent models of muscle atrophy include mechanical unloading, which reversibly affects a broad range of muscle groups, and surgical denervation of target muscles, which is generally irreversible absent surgical reinnervation. Botulinum neurotoxins (BoNT) are bacterial toxins that cause muscle paralysis by preventing acetylcholine release at the neuromuscular junction. Because BoNT produces reversible paralysis, we hypothesized that BoNT would be a promising candidate for studying the molecular markers associated with atrophy. Intramuscular (IM) injection of the mouse extensor digitorum longus (EDL) muscle by BoNT serotype A (BoNT/A) produces full paralysis within three days, as monitored by the semi-quantitative digit abduction score (DAS). Intoxication persists for approximately two weeks before resolving. In preliminary studies, BoNT/A-intoxicated EDL muscles undergo morphological changes characteristic of atrophy by 8 days after intoxication, evidenced by reduced muscle mass and fiber diameter. In therapeutic studies, subcutaneous (SC) injection of 3,4-diaminopyridine (DAP) (TID, 2 mg/kg) from 3-9 days after intoxication significantly attenuated muscle wasting. Moreover, the muscle sparing effect could be fully replicated in a dose-dependent manner by once-daily DAP treatments from 3-5 days after intoxication. These data suggested that IM administration of BoNT/A causes muscle atrophy which can be attenuated by short-term and partial reversal of paralysis over a narrow window of time. To further understand the mechanisms involved in atrophy and recovery, we conducted a mouse study to (a) characterize the impact of BoNT intoxication on molecular markers of atrophy and (b) correlate changes in molecular markers with functional improvements in DAS after DAP treatment. Female CD1 mice were injected IM in the extensor digitorum longus (EDL) with 1.25 mouse lethal dose 50 (LD50) units of BoNT/A (n = 16) and treated SC with 2 mg/kg DAP (n = 8) or saline (n = 8) 3-5-days post intoxication and harvested on day 8 for transcriptomic analysis. Mice were assessed daily for clinical signs and symptoms of botulism and Digit Abduction Score (DAS). Daily DAP injected days 3-5 post intoxication was observed to significantly reduce DAS severity through day 7 relative to the control, and treated mice were observed to more regularly utilize their intoxicated hindlimb relative to the vehicle controls. These results, coupled with forthcoming transcriptomic data, indicate that BoNT/A and DAP comprise a titratable, non-invasive atrophy model.

Disclosures: T.G. Wentz: None. **Z.D. Chandler:** None. **P.M. McNutt:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.19/F26

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

Title: Cocaine causes neuroinflammation, altered neurotrophic signalling and aberrant neuroplasticity mechanisms of damage in a human induced pluripotent stem cell-derived cerebral organoid model of cocaine-mediated neurodevelopmental perturbation

Authors: *L. KEEGAN[1], J. DAVIS[2], C. KENNEDY[3], C. MC MAHON[4], N. TREACY[4], S. CLERKIN[5], Y. KELLY[4], K. J. MURPHY[5], J. CREAN[5];
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Abstract: Cocaine addiction is an ever-increasing, devastating disorder and a significant global public health issue. Prenatal exposure to cocaine has significant effects on foetal brain growth and neurological development, potentially resulting in long-term behavioural and intellectual disabilities. Previous studies in rodent models have indicated that prenatal cocaine exposure affects proliferation, differentiation, and connectivity of neural cell types. Here, using human iPSC-derived cerebral organoids, we investigated cocaine-induced changes of the gene expression regulatory landscape, leveraging recent advances in single cell RNA-seq and single cell ATAC-seq. iPSC-cerebral organoids modelled well-established cocaine responses observed in vivo. In addition, the data provided additional insights into the cell-type specific regulation of gene expression following cocaine exposure. Cocaine altered gene expression patterns, in part through epigenetic landscape remodelling, revealing altered neural plasticity mechanisms in the cerebral organoids. Perturbed neurodevelopmental cellular signalling and an inflammatory-like activation of astrocyte populations were also evident following cocaine exposure. The combination of altered neuroplasticity, neurodevelopment and neuroinflammatory signalling suggests cocaine exposure can mediate substantial disruption of the normal development and maturation of the brain. These findings offer new insights into the cellular mechanisms underlying the adverse effects of cocaine exposure on neurodevelopment and the possible pathomechanisms of later neuropsychiatric disturbances.

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.20/F27

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

Support: NIH/NIDCR Grant R01DE22032

Title: Correlative microspectroscopy of spatially co-localized zinc, oxidative stress, and neurovascular invasion in temporomandibular joint osteoarthritis patients

Authors: *B. H. LEE[1,3], H. CI[4,1], Z. YANG[1,5], Y. WANG[1], N. TAMURA[6], D. PARKINSON[6], S. CONNELLY[7], S. WEBB[8], S. HO[1,2];
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Abstract: Neurovascular invasion is a pathologic marker of osteoarthritis (OA). We hypothesize that chronic mechanical loads affect neurovascular invasion at the osteochondral interface (OCI) in temporomandibular joint OA (TMJ OA) through zinc-mediated oxidative pathways and alter the biomineralogy of the OCI. Our objective is to spatially colocalize zinc (Zn), reactive oxygen species (ROS), and neurovascular bundles with OCI mineral densities. Frozen condyles (N=3) from TMJ OA patients were used to spatially colocalize Zn, calcium, phosphorus, and sulfur (S) species using X-ray absorption spectroscopy. Spatial maps of oxidized (glutathione disulfide) and reduced (glutathione) S species were generated to confirm oxidative stress in higher and lower Zn regions. Mineral densities and vasculature were determined with micro-CT, and crystallinities were identified by X-ray diffraction. Tissues were immunolocalized for platelet endothelial cell adhesion molecule (CD31) - blood vessels; neuron nuclear protein (NeuN) and protein-gene product 9.5 (PGP 9.5) - neurons; PIEZO1 and TRPV4 - mechanosensory ion channels; and calcitonin gene-related peptide (CGRP) and hypoxia-inducible factor 1α (HIF-1α) - ROS. Distinct bands of Zn-incorporated hydroxyapatite and Zn-phosphate in the OCI were identified. HIF-1α was strikingly higher in bone and reduced in cartilage. Small diameter channels as visualized with micro-CT were CD31 positive. Colocalization of NeuN, PGP 9.5, and CGRP indicated OCI hyperinnervation. Increased PIEZO1, decreased TRPV4 expressions, and decreased GSH to GSSG ratios (7.8±0.3) were observed. Quantitative spatial maps of Zn and S species provided insights into a two-event mechanistic pathway. The primary event of a differential shift in the partial pressure of oxygen, stimulated by aberrant mechanical forces on cartilage, encourages an oxidative pathway catalyzed by Zn and ROS influxes which are cues for neurovascular invasion. The secondary event of persistent oxidative stress at the OCI results in pathologic zinc-abundant biominerals.

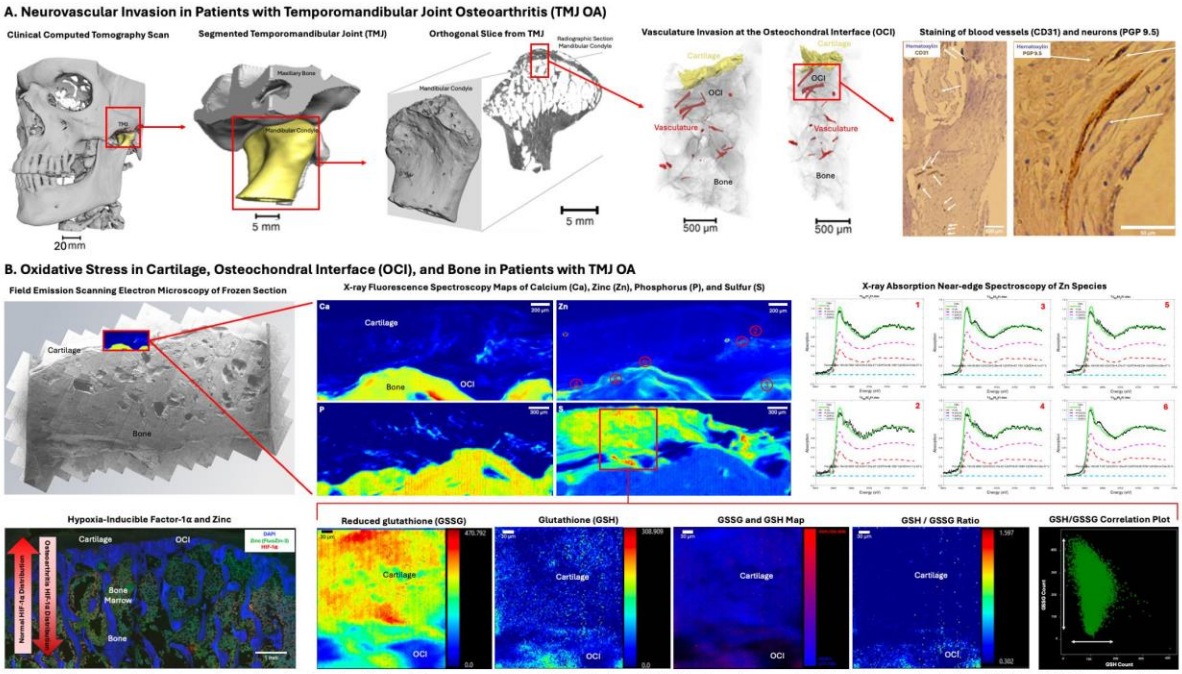

Figure 1. A) Neurovascular invasion and pathobiomineralogy in patients with temporomandibular joint (TMJ) osteoarthritis. Blood vessels segmented in the TMJ. Immunolocalization of CD31 and PGP 9.5 confirmed blood vessels and nerves. **B. Oxidative stress in cartilage, osteochondral interface, and bone.** Field emission scanning electron microscopy shows morphology of TMJ slice and location for X-ray fluorescence spectroscopy. Spatial maps of calcium, zinc, phosphorus, and sulfur are shown. Zinc species (zinc-incorporated hydroxyapatite, zinc-phosphate, zinc-sulfate, zinc-carbonate) were identified at locations 1-6. Oxidative stress shown by staining with hypoxia inducible factor-1α is confirmed by the ratio of reduced glutathione (GSH) to glutathione disulfide (GSSG, oxidized).

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Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.21/F28

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

Support: CONAHCYT Grant 1252820
U. de G. PIN 2021-11 to L.H.
U. de G. ProSNI 2023 to L.H.

Title: Study of serotonergic neurotransmission dependent Egg-laying behavior and the stress response protein HSP-16.2 expression in Caenorhabditis elegans infected by Enteropathogenic Escherichia coli and Salmonella Typhimurium

Authors: *D. AGUILAR OCAMPO[1], A. CASTILLO-ROMERO[1], L. A. RAMIREZ CONTRERAS[2], S. A. GUTIERREZ-RUBIO[3], G. CAMARGO HERNÁNDEZ[4], L. HERNANDEZ[5], T. A. GARCIA[6];
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Abstract: Introduction: There is a bidirectional communication pathway between the nervous system and the gut microbiota: the microbiota-gut-brain axis. Infection-induced gut dysbiosis may contribute to neuropsychiatric manifestations by disrupting neurotransmitter homeostasis. Thus, alterations in GABAergic and serotonergic neurotransmission are of interest in the context of bacterial infections, including those caused by enteropathogenic *Escherichia coli* and *Salmonella* Typhimurium. Unfortunately, the complexity of the nervous system and the diversity of the gut microbiota in mammals hinder the understanding of their interaction. Fortunately, this can be studied in a simpler and well-defined model, the nematode Caenorhabditis elegans, which is widely used in studies of microbial pathogenesis and has a simple nervous system that includes the GABAergic and serotonergic systems. We also hypothesize that bacterial infection and subsequent intestinal dysbiosis induce oxidative stress and that the response to this stress could influence the severity of CNS damage induced by the infection of diarrheagenic bacteria. **Aim:** To evaluate the effect of enteropathogenic *Escherichia coli* and *Salmonella* Typhimurium infection on GABA- and serotonin-dependent stereotypic behaviors and the stress response in *Caenorhabditis elegans*. **Methods:** *C. elegans* N2 Bristol (WT) and TJ375 (gpIs1 [hsp-16.2p::GFP]) strains were divided into 3 groups, a CONTROL group fed with their standard chow, *E. coli* OP50, an EPEC group fed with enteropathogenic *Escherichia coli*, and a STyp group fed with *Salmonella* Typhimurium. On days 1, 2 and 3 of infection, was quantified the Egg-laying, which is serotonergic neurotransmission dependent. Also, TJ375 worms (which inducibly expresses the protein HSP-16.2) were mounted on a 2% agarose pad placed on a slide. They were subsequently observed in an epifluorescence microscope. **Results.** With EPEC, Egg laying decreased by 28%, 68%, and 78% on days 1, 2, and 3, respectively, compared to the control. With Styp this decrease was 50%, 61% and 83% on the corresponding days 1, 2 and 3. The protein HSP-16.2 is indicative of free radicals' presence and play a part in the endogenous response to oxidative stress. Thus, we found that EPEC increase 110% the HSP-16.2, while Styp decreased 65%. **Conclusions:** The results suggest that both pathogenic bacteria decrease serotonergic activity in a time-dependent manner. Also, a higher expression of HSP-16.2 in EPEC worms could suggest a mechanism of action that involves higher levels of free radicals, which would be different than Styp.

Disclosures: D. Aguilar Ocampo: None. **A. Castillo-Romero:** None. **L.A. Ramirez Contreras:** None. **S.A. Gutierrez-Rubio:** None. **G. Camargo Hernández:** None. **L. Hernandez:** None. **T.A. Garcia:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.22/F29

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

Support: CONAHCYT PSBR/960407
EDGM/1270602
University of Veracruz Proyect 10480202266
Academic Group of Neurochemistry (UV-CA 304)

Title: Analysis of immune infiltrate, histology, serum cytokine and hormonal profile in the denervated prostate

Authors: *P. BECERRA-ROMERO[1], E. GARCIA[2], C. FERNÁNDEZ-POMARES[2], F. ROJAS-DURÁN[3], R. TOLEDO-CARDENAS[2], D. HERRERA-COVARRUBIAS[2], G. E. ARANDA-ABREU[6], J. MANZO[4], G. A. CORIA-AVILA[5], M. HERNANDEZ[3];
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Abstract: The prostate, an accessory sexual gland in male reproduction, is regulated by both the endocrine system and the autonomic nervous system. Preganglionic fibers from the viscerocutaneous branch of the pelvic nerve and the hypogastric nerve converge in the major pelvic ganglion, from which postganglionic innervation to the prostate arises. Recent studies have shown the presence of inflammatory infiltrates in this gland in response to preganglionic axotomy. Therefore, the fundamental purpose of this research was to characterize the type of infiltrate present in the denervated prostate, the types of cytokines present, and their correlation with prostatic histology. For this, male rats weighing 300 grams were subjected to preganglionic axotomy and left for a period of 15 days. The weight of each prostatic lobe was measured, immune populations were characterized through flow cytometry, proinflammatory and anti-inflammatory cytokines, testosterone and prolactin were quantified by ELISA, and the prostatic tissue was stained with Hematoxylin-Eosin for histological analysis. The results showed a decrease in the weight of both prostatic lobes because of preganglionic injury to the pelvic and hypogastric nerves. The presence of leukocytes, macrophages, B lymphocytes and T lymphocytes, (CD3+, CD4+ and CD8+) was identified in the infiltrate, along with an increase in serum levels of testosterone, prolactin and interleukins IL-1β, IL-6, IL-10, and IFN-γ. Additionally, the presence of hyperplasia and metaplasia in response to the axotomy of these nerves was evidenced, and axotomy of the hypogastric nerve also induced an increase in the infiltrate of neutrophils. Taken together, these results indicate that the loss of nervous control leads to an inflammatory process, along with histological changes and the loss of prostatic cells. This suggests that prostatic lesions are not exclusively the result of hormonal alterations, but that the nervous and immune components also play a crucial role in this process. These findings provide a new perspective for approaching prostatic diseases.

Disclosures: P. Becerra-Romero: None. **E. Garcia:** None. **C. Fernández-Pomares:** None. **F. Rojas-Durán:** None. **R. Toledo-Cardenas:** None. **D. Herrera-Covarrubias:** None. **G.E. Aranda-Abreu:** None. **J. Manzo:** None. **G.A. Coria-Avila:** None. **M. Hernandez:** None.

Poster

PSTR124: Neuroimmune Mechanisms of Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR124.23/F30

Topic: B.09. Glial Mechanisms

Support: NARSAD Brain and Behavior Foundation
Quinnipiac College of Arts and Sciences

Title: Behavioral Effects and transcriptional signatures of CD-11b+ microglia in Chronic Unpredictable Stress

Authors: C. SIPPER[1], M. L. ROSE[1], P. WOLUJEWICZ[1], *A. BETZ[2];
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Abstract: Microglial activation is pivotal in the neuroinflammatory processes underlying various central nervous system (CNS) disorders. Chronic psychological stress detrimentally affects immune system function. Chronic Unpredictable Stress (CUS) animal models induce a range of unpredictable stressors over an extended period, mimicking aspects of human stress-related disorders. Behavioral manifestations include alterations in mood, cognition, and social behavior, mirroring clinical symptoms. Initially, we assessed the behavioral ramifications of CUS in male Sprague-Dawley rats over 21 days. Following stress induction, rats were sacrificed, and single-cell dissociations from the hippocampus and prefrontal cortex were performed. Highly purified CD11-b microglia were obtained via immunomagnetic isolation and validated using flow cytometry. Transcriptional analyses were conducted in these brain regions on these specific cells. In the hippocampus (HPC), differential expression analysis revealed significant upregulation of the Fkbp5 gene—a crucial stress-inducible gene with a pivotal role in glucocorticoid receptor complex regulation and intracellular glucocorticoid signaling. Principal Component Analysis (PCA) further delineated stress-induced alterations in gene expression profiles. In the prefrontal cortex (PFC), Tsc22d2 was significantly upregulated, associated with cell cycle regulation, and implicated in inhibited cell growth under stress conditions. Conversely, Clec14a exhibited significant downregulation. These findings underscore the intricate interplay between stress, gene expression modulation, and neuroinflammation within distinct brain regions and distinct cell types. Understanding the complexities of CUS offers valuable insights into stress-related psychopathologies and informs the development of novel therapeutic interventions.

Disclosures: C. Sipper: None. **M.L. Rose:** None. **P. Wolujewicz:** None. **A. Betz:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.01/F31

Topic: F.07. Biological Rhythms and Sleep

Title: Consumption of a high-fat diet alters behavioral and physiological outcomes in Swiss Webster mice exposed to a Mars solar day

Authors: M. MILANO, C. MURPHY, S. TADROS, G. GUINDON, *J. A. SEGGIO;
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Abstract: Many world governments and one prominent businessman believe that the future of humanity lies in the colonization of Mars. Mars has a daylength of 24 hours and 40 minutes. Previous work has shown that altering daylength can lead to desynchronization of the circadian clock, leading to negative behavioral and physiological outcomes. Additionally, consumption of a high-fat diet is also known to lead to behavioral issues and disrupt the circadian rhythm. The purpose of this study was to investigate whether placement into a Mars-day period leads to alterations in circadian and novelty-induced locomotion, and if consumption of high-fat diet modulates these outcomes. Male and female Swiss webster mice were given either regular (RC) or high-fat chow (HF). Afterwards, mice were placed into circadian activity monitoring cages under either a standard earth-like 24-hour, 12:12 light:dark cycle (E) or a mars-like 24.66 hour, 12.33:12.33 light:dark cycle (Mars). As such there were four groups for each sex: 1) HF/Mars, 2) HF/Earth, 3) RC/Mars, and 4) RC/Earth. Circadian rhythms, fasting glucose, and anxiety-like behaviors were assessed for each mouse. All mice, except two female Mars/HF, were able to entrain to their respective photoperiods; as such these mice had a statistically significantly higher chance of not being entrained to the Mars photoperiod. Additionally, while E/HF mice exhibited increased circadian power and reduced locomotor activity compared to Mars/HF, no differences were observed between the two diets on an Earth photoperiod. Novelty-induced locomotion in the open field was reduced in Mars mice compared to Earth mice. Additionally, female Mars mice consuming HF exhibited decreased velocity in the light zone compared to female mice consuming HF in an Earth-day. Lastly, female Mars mice exhibited reduced fasting glucose compared to male Mars, while no differences were observed for mice in the Earth-like photoperiod. In summary, mice exposed to a Mars day exhibited reduced circadian robustness and reduced exploratory activity. As reductions in circadian robustness is linked to increased prevalence of emotional disturbances, individuals under a Mars photoperiod may be prone to developing emotionality issues and may exacerbate the symptoms of existing mood disorders. These results also indicate that consumption of HF may lead to issues when exposed to non-24-hour daylengths and that, surprisingly, females maybe more susceptible to those changes.

Disclosures: M. Milano: None. **C. Murphy:** None. **S. Tadros:** None. **G. Guindon:** None. **J.A. Seggio:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.02/F32

Topic: F.07. Biological Rhythms and Sleep

Title: Sex differences in the behavioral responses to constant light and SKF-38393 (D1R agonist) consumption in C57BL/6J mice

Authors: *G. GUINDON, S. TADROS, M. MILANO, C. MURPHY, J. A. SEGGIO;
Biol. Sci., Bridgewater State Univ., Bridgewater, MA

Abstract: Disruptions to the circadian rhythm have been shown to lead to alterations in depression-like behaviors and motivation. Additionally, dopamine, the major reward neurotransmitter, is controlled by the biological clock and circadian desynchronization can lead to alterations in dopamine signaling. This investigation aimed to uncover the behavioral effects of SKF-38393 consumption, a Dopamine-1-receptor agonist (DA), on male and female C57BL/6J mice in constant light (LL). As such, there were four groups for each sex: 1) LD/Water, 2) LL/Water, 3) LD/DA, 4) LL/DA. All mice had their fluid consumption measured and were subjected to open field, novel object, and sucrose preference tests to assess exploration, memory, and depression-like behaviors. Overall, female mice consumed more DA compared to males, while water consumption remained similar. Additionally, while male mice in LL reduced their DA consumption over the course of the experiment, female mice in LL did not, nor did male mice in LD. F/LL/DA mice also exhibited decreased sucrose preference compared to M/LL/DA mice. Additionally, LL reduced sucrose preference for males consuming water but not DA. Female mice in LL exhibited reduced open field explorative behaviors in LL compared to male mice, although DA consumption prevented this behavioral change. Additionally, after multiple trials in the novel object assay, F/LL mice exhibited increased interactions with the objects compared to F/LD mice. However, male mice in LL exhibited poorer memory via reduced interactions with the new object compared to male mice in LD and female mice. These results indicate that male mice are more sensitive to the negative cognitive effects of LL, while female mice are more sensitive to explorative effects of LL. Furthermore, DA consumption prevented anhedonia-like symptoms in male mice. Female mice may also have increased sensitivity in their reward pathway as they showed increased DA consumption and sucrose consumption under DA compared to male mice.

Disclosures: G. Guindon: None. **S. Tadros:** None. **M. Milano:** None. **C. Murphy:** None. **J.A. Seggio:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.03/F33

Topic: F.07. Biological Rhythms and Sleep

Support: NIH grant F31 EY034387
NSF grant DGE-1842165
NIH grant 1DP2EY022584

Title: Sex-dependent modulation of visual behaviors by the ipRGC molecular clock

Authors: *K. MIGUEL[1], J. BHOI[2], G. DYER[1], C. P. RIBELAYGA[3], T. M. SCHMIDT[2]; [1]Northwestern Univ., Evanston, IL; [2]Neurobio., Northwestern Univ., Evanston, IL; [3]Univ. of Houston, Houston, TX

Abstract: Circadian rhythms control many aspects of animal physiology, including modulating sensitivity to sensory stimuli. However, little is known about how peripheral molecular clocks in sensory organs might play a role in this modulation. Here, we investigate whether cell-autonomous clocks in the retina contribute to observed rhythms in visual behaviors in mice. Intrinsically photosensitive retinal ganglion cells (ipRGCs) are a population of retinal cells that express the photopigment melanopsin (Opn4) and contribute to several visual behaviors, some of which are known to be subject to circadian modulation. ipRGCs contain cell-autonomous clocks, and we hypothesize that it is these cellular clocks within ipRGCs that drive the circadian modulation of these behaviors. To test this, we measured various ipRGC-driven behaviors in $Opn4^{cre/+}$; $Bmal1^{fx/fx}$ (Bmal1 cKO) mice, in which the core circadian clock gene Bmal1 is knocked out of ipRGCs exclusively. Our data show that disruption of the ipRGC clock results in deficits in these behaviors, suggesting that the ipRGC clock is necessary for the normal visual function. Additionally, we find that these behavioral deficits are sex dependent. ipRGC function relies partially on the expression of melanopsin, which is known to be rhythmic. We used whole retina qPCR to measure the expression of melanopsin in male and female control and Bmal1 cKO mice at four circadian time points. We find that the normal rhythmic expression of melanopsin is altered in Bmal1 cKO mice. Overall, our findings suggest an important and sex-dependent role for the ipRGC molecular clock in modulating the both expression of melanopsin and the sensitivity of ipRGC-driven behaviors.

Disclosures: K. Miguel: None. **J. Bhoi:** None. **G. Dyer:** None. **C.P. Ribelayga:** None. **T.M. Schmidt:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.04/F34

Topic: F.07. Biological Rhythms and Sleep

Support: R01AT011439

Title: Phase dependent melatonin administration acutely increases the glymphatic influx of healthy anesthetized mice

Authors: *V. S. VIZCARA[1], Y. ZHU[2], E. DUYVESTEYN[2], M. NEDERGAARD[3], L. M. HABLITZ[4];
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Abstract: The glymphatic system clears metabolic waste from the brain via cerebrospinal and interstitial fluid movement through a network of perivascular spaces surrounding the brain's vasculature. Glymphatic influx can be modulated with anesthetics, or by non-pharmacological factors such as sleep. However, there are currently no known pharmacological means to improve glymphatic function. The glymphatic system has an endogenous circadian rhythm, with increased influx and solute clearance during the rest phase. Thus, drugs that can influence circadian rhythms may modulate of glymphatic function. Melatonin is a light-sensitive hormone known to regulate circadian timing. Because of its chronobiotic characteristics, melatonin has emerged as a likely pharmacological agent for glymphatic modulation. Here, we asked if acute and chronic melatonin (90 µg/mouse, s.c.) administration affects the glymphatic influx of healthy awake and anesthetized mice at different times of day. We used CSF tracer infusions in the cisterna magna and ex vivo brain slice imaging to evaluate glymphatic influx of CSF into the brain of mice after their designated treatment. Our results show increased glymphatic flow in anesthetized mice receiving acute melatonin two hours before lights off, when it impacts circadian timing the most. However, this appears to normalize after two-week administration. We conclude that melatonin may be useful as an acute pharmacological target for modulation of glymphatic function. These results support the hypothesis that improvement or preservation of circadian rhythms might provide a way to improve glymphatic function. Future work needs to be done to evaluate the potential of melatonin as a therapeutic target for glymphatics in aged or diseased states, where both circadian timing and glymphatic function are impaired.

Disclosures: V.S. Vizcara: None. **Y. Zhu:** None. **E. Duyvesteyn:** None. **M. Nedergaard:** None. **L.M. Hablitz:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.05/F35

Topic: F.07. Biological Rhythms and Sleep

Support: NSF Grant 1736019

Title: The effects of dibutyl phthalate developmental exposure on stability of worker honey bee circadian rhythms

Authors: *C. RODRIGUEZ ALEMANY[1], M.-E. PEREZ-HERNANDEZ[2], J. L. AGOSTO[1], T. GIRAY[1];
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Abstract: Honey bees (*Apis mellifera*) are economically and ecologically important plant pollinators that are highly and constantly exposed to environmental stressors including chemical pollutants, which have been linked as one source of honey bee colony losses. Stressor's impact the bees' complex behaviors, social organization, and division of labor that are regulated by circadian clocks and the rhythms they generate. Honey bees as bioindicators of environmental pollution are an excellent model to study the impact of ubiquitous chemical pollutants such as dibutyl phthalate (DBP) on the circadian rhythmicity ontogeny and plasticity and adult behavioral development of newly emerged workers. Here, the locomotor activity of worker bees, chronically exposed to different sublethal DBP concentrations during their larval or adult stages, was constantly recorded for a period of 15-20 days to determine the effects of DBP on circadian rhythmicity and behavior. Chronic oral exposure to DBP throughout development affected adult locomotor activity levels, timing, and duration. Nonetheless, DBP ingestion did not influence the periodicity and strength of the circadian rhythms of adult worker bees. Our results indicate that environmental DBP stress exposure influences worker honey bee circadian system and behavioral development.

Disclosures: C. Rodriguez Alemany: None. **M. Perez-Hernandez:** None. **J.L. Agosto:** None. **T. Giray:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.06/F36

Topic: B.05. Synaptic Plasticity

Support: JSPS 23K27354
JSPS 23K18147
JSPS 20H05903

Title: Understanding the role of cell cycle checkpoint activation in sleep homeostasis

Authors: *H. YAMASAKI[1], S. NOMURA[1,2], C. SHIMIZU[1], Y. LUO[1], S. SHI[1];
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Abstract: Sleep is a conserved behavior among a broad range of species. Its significant role in homeostasis ensures a consistent duration of sleep each day, and the biological basis of sleep homeostasis remains a key question in sleep research. The accumulation of insights from the role of synaptic potentiation, metabolite concentrations, and phosphorylation of synaptic proteins on sleep regulation has suggested that fundamental cellular components and functions of neurons play a crucial role in the regulation of sleep need. Recent studies have demonstrated that DNA

damage accumulates in the neurons of zebrafish larvae during wakefulness and is repaired during sleep, which promotes homeostatic sleep pressure.In this study, we investigated the role of cell cycle checkpoint activation in sleep regulation by using in vitro dissociated cortical neuron system and mice. We explored whether the tumor suppressor p53, which is involved in cell cycle arrest, regulates sleep in response to DNA damage accumulated in neurons during wakefulness. Interestingly, activation and inhibition of the p53 pathway in mice resulted in bidirectional changes in sleep duration as well as delta power. Neurons are generally considered post-mitotic cells that remain in the G0 phase of the cell cycle. Upon DNA damage, p53 can counteract neuronal cell cycle re-entry by promoting DNA repair and inhibiting cell cycle progression. Therefore, our results suggest that a p53-dependent cell cycle arrest mechanism may play a role in both neuronal maintenance and sleep homeostasis.

Disclosures: H. Yamasaki: None. **S. Nomura:** None. **C. Shimizu:** None. **Y. Luo:** None. **S. Shi:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.07/F37

Topic: B.05. Synaptic Plasticity

Support: JSPS 21K20683, 23K14285, 20H05894, 20H05903, 21K15136, 22K21351, 23H02518A, 23H02663, 23K18147, 23K14282 and 20H05685
JST JPMJAX2116, JPMJCR21E2 and JPMJMI22J5
AMED JP21zf0127005 and JP15dm0207001
the Chugai Foundat ion and the Japan Foundation for Applied Enzymology
the Tokyo Society of Medical Sciences
the Top Runners in Strategy of Transborder Advanced Researches (TRiSTAR) by the MEXT

Title: A synapse chemogenetic tool to elucidate the regulation of sleep need by prefrontal synaptic strength

Authors: *T. SAWADA[1,2,3,5], Y. IINO[6], K. YOSHIDA[8,5], H. OKAZAKI[4], S. NOMURA[6,2], T. ARIMA[2], T. SAKURAI[7,5], S. YAGISHITA[2,3], M. YANAGISAWA[6], T. TOYOIZUMI[8], S. SHI[6], H. KASAI[4];
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Abstract: Sleep is regulated through a homeostatic need, which accumulates during wakefulness and dissipates during sleep; synaptic strength of cortical neurons has been implicated as a key

component of sleep homeostasis. During non-rapid eye movement (NREM) or slow-wave sleep, characterized by a low-frequency and high-amplitude EEG, the EEG delta power serves as the primary marker of sleep need. However, there remains a significant gap in understanding the causal relationship between cellular-level synaptic strength and macro-level delta power in the context of sleep homeostasis. In this study, we developed a novel molecular tool, SYNCit-K, which utilizes chemically induced dimerization to accumulate the guanine nucleotide exchange factor (GEF), Kalirin7, into the dendritic spines. It induced spine enlargement and long-term potentiation (LTP) in both dissociated cortical neurons, hippocampal slice cultures and mouse primary visual cortex (V1) in vivo. Notably, synaptic potentiation by SYNCit-K in excitatory neurons in the prefrontal cortex (PFC), but not in the V1, increased both the amount and EEG delta power of NREM sleep, which is also observed after pharmacological positive modulation of AMPA receptors. Furthermore, we utilized an excitatory-inhibitory neural network model to predict that an increase in excitatory synaptic strength in cortical excitatory neurons induces periodical hyperpolarized inactive periods (down state), leading to an elevation in simulated delta power. Therefore, we propose a new chemogenetic tool SYNCit-K to induce LTP and a regulatory mechanism whereby sleep need is encoded in the synaptic strength of PFC excitatory neurons, and that this, in turn, promotes deeper NREM sleep.

Disclosures: T. Sawada: None. **Y. Iino:** None. **K. Yoshida:** None. **H. Okazaki:** None. **S. Nomura:** None. **T. Arima:** None. **T. Sakurai:** None. **S. Yagishita:** None. **M. Yanagisawa:** None. **T. Toyoizumi:** None. **S. Shi:** None. **H. Kasai:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.08/G1

Topic: B.05. Synaptic Plasticity

Title: Understanding the link between DNA damage response pathways and neuronal slow wave activity through synaptic plasticity

Authors: *S. NOMURA[1,2], H. YAMASAKI[2], K. YOSHIDA[3,2,1], T. SAWADA[1], Y. IINO[2], H. KASAI[1], S. SHI[2];
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Abstract: Current evidence suggests that the regulation of cortical neurons at the cellular level, including factors such as synapse potentiation, DNA damage, and oxidative stress, affects sleep. In this study, we used a mathematical model and a multi-electrode array (MEA) to investigate whether these cellular-level factors play a role in sleep regulation and homeostasis. Initially, we investigated whether synaptic potentiation triggers sleep using a two-population mathematical model composed of excitatory and inhibitory neuronal populations. Our model demonstrates that synaptic potentiation among excitatory neurons can facilitate the transition from awake-like

firing to sleep-like firing patterns. Detailed mathematical analysis revealed that this transition is facilitated through the destabilization of the up-state, known as a Hopf bifurcation. To validate the predictions from the mathematical model, we utilized an MEA system. The administration of a positive allosteric modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor to dissociated cortical neurons on MEA induces synchronized sleep-like firing patterns and increase delta power, a promising marker of sleep need, in the local field potential. We then focused on the effects of DNA damage pathway on synaptic potentiation and sleep regulation by pharmacologically targeting p53 and other DNA-damage response proteins, examining their potential effects on neural firing properties. The effects of pharmacological perturbation were also validated in vivo with sleep recordings. As a result, we found that p53 and its downstream pathways play a significant role in sleep regulation and homeostasis. In summary, our study proposes a novel cellular mechanism for sleep regulation, bridging the gap between intracellular DNA damage responses and sleep induction at the organismal level.

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Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.09/G2

Topic: F.07. Biological Rhythms and Sleep

Support: NIH 1R21MH131527-02

Title: Clock-aligned increases in state-specific spectral frequency power in diurnal rodents

Authors: *J. HARTNER[1], B. O. WATSON[2];
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Abstract: Increasing evidence links circadian rhythm, sleep, and mood disorders in humans. Understanding and treating these disorders requires better understanding of circadian modulation of neural circuits. Differences between nocturnal and diurnal rodent brain biology have been shown to be more complex than an inverted daily pattern; however, most rodent research is done on nocturnal species, resulting in unclear translational implications for human disease. Nile Grass Rats (NGRs) are an established diurnal rodent model well-suited for studying circadian dynamics and bridging the gap between nocturnal rodents and humans. NGRs have been shown to exhibit reversal of daily movement profiles compared to nocturnal rodents, but it is unclear how neural circuitry and network activity differs between the species. NGRs have also been shown to exhibit depression-like behavior following altered lighting conditions and circadian misalignment, similar to human Seasonal Affective Disorder (SAD) and Major Depressive Disorder (MDD).

To better understand circadian modulation of neural networks and its implications for psychiatric and mood disorders, we implanted silicon recording probes in the medial prefrontal cortex (mPFC) and CA1 of the dorsal hippocampus (HC) and performed chronic weeks-long electrophysiological recordings in varying light conditions. Early findings show that NGRs exhibit diurnal activity patterns, and also show an increase in movement under bright light (>1000 Lux) during the lights-on period. We see an unexpected lack of circadian modulation of sleep-wake state time/proportion, though REM sleep seems most strongly modulated. We are currently investigating whether bright light exposure can modulate either or both spectral power network activity as well as individual neuronal spiking across sleep and wake states. Further, we plan to investigate if bright light can rescue the depressive effects on movement and brain activity in animals subjected to disrupted light cycles and/or dim (<50 Lux) lighting for extended periods. This work can help validate the translation of sleep and circadian rhythms findings from nocturnal animals to human disease while also highlighting the need for more research in diurnal animal models to better understand and treat circadian rhythm, sleep, and depression disorders in humans.

Disclosures: J. Hartner: None. **B.O. Watson:** None.

Poster

PSTR125: Circadian Rhythms and Sleep

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR125.10/G3

Topic: F.07. Biological Rhythms and Sleep

Title: Establishment of the new mice model of circadian rhythm sleep-wake disorder (CRSWD) and search for its treatment

Authors: *K. KOZUKA, R. EGAMI, K. KUME;
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Abstract: The two-oscillator hypothesis is proposed as a mechanism for generating sleep-wake rhythms. In this hypothesis, the sleep-wake rhythm is explained by the interaction between oscillator I, which drives the suprachiasmatic nucleus (SCN)-dependent circadian rhythm, and oscillator II, which mainly drives sleep-wake rhythm independent of the SCN. These two rhythms are normally synchronized, but when they desynchronize and become a state called internal desynchronization, sleep-wake free-runs with oscillator II, resulting in a longer period. Circadian rhythm sleep-wake disorder (CRSWD) causes social problems because the patient's sleep-wake rhythm deviates from the normal day-night rhythm. Recent studies showed that one-third or more of CRSWD patients have normal melatonin rhythms, but their sleep phase is sifted, raising the possibility that some CRSWD patients may have internal desynchronization. However, until now, no appropriate animal model for this situation has been available. Here, we established a mouse model of CRSWD. Specifically, we placed a flat running wheel in the rearing environment to increase motivation for spontaneous activity. We also chronically

administered low concentrations of methamphetamine to prolong wake time in order to reproduce the human pathological state. We then attempted to treat the mice with aripiprazole, a dopamine D2/D3 receptor partial agonist. It is broadly used as an antipsychotic in psychiatry and is recently started to be applied to CRSWD. Furthermore, we investigated the effect of aripiprazole to promote entrainment to the phase shift in an 8-hour phase-advance jet-lag experiment. As a result, we found that administration of aripiprazole to CRSWD mice model synchronized their sleep-wake rhythm to the light-dark cycle. Moreover, we confirmed that this entrainment was accompanied by changes in sleep architecture. Furthermore, we found that administration of aripiprazole to mice model of jet lag showed advancing effects on the waking time. Our results may provide a stepping stone to understanding the pathogenesis of CRSWD with internal desynchronization and suggest that aripiprazole target modification of sleep-wake rhythms rather than circadian rhythms.

Disclosures: K. Kozuka: None. **R. Egami:** None. **K. Kume:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.01/G4

Topic: G.01. Fear and Aversive Learning and Memory

Support: GNT2011633
DP220100040

Title: Basolateral amygdala output pathways during fear learning

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Abstract: The presence of valence coding neurons in the basolateral amygdala (BLA) that form distinct projections to other brain regions implies functional opposition between aversion and reward during learning. However, evidence for opponent interactions in fear learning is sparse and may only be apparent under certain conditions. Here we test this possibility by studying the roles of the BLA-central amygdala (CeA) and BLA-nucleus accumbens (Acb) pathways in fear learning in male rats. First, we assessed the organisation of these pathways in the rat brain. BLA-CeA and BLA-Acb pathways were largely segregated in the BLA but shared overlapping molecular profiles. Then we assessed activity of the BLA-CeA and BLA-Acb pathways during two different forms of fear learning - fear learning in a neutral context and fear learning in a reward context. BLA-CeA neurons were robustly recruited by footshock regardless of where fear learning occurred whereas recruitment of BLA-Acb neurons was state-dependent because footshock only recruited this pathway in a reward context. Finally, we assessed the causal roles of activity in these pathways in fear learning. Photoinhibition of the BLA-CeA pathway during the footshock US impaired fear learning, regardless of where fear learning occurred. In contrast,

photoinhibition of the BLA-Acb pathway augmented fear learning, but only in the reward context. Taken together, our findings show circuit- and state-dependent opponent processing of fear. Footshock-driven activity in the BLA-Acb pathway can functionally oppose the BLA-CeA pathway to limit how much fear is learned.

Disclosures: J.O.Y. Yau: None. **G.P. McNally:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.02/G5

Topic: G.01. Fear and Aversive Learning and Memory

Support: STI2030-Major Projects 2022ZD0207500

Title: Basolateral Amygdala Axo-axonic Inhibition in Associative Learning

Authors: Y. ZHOU[1], P. MA[1], W. QU[1], Z. HE[1], M. WU[1], M. HE[2], Y. TAI[3], J. LU[4], L. LIN[1], ***Y. GU**[1];
[1]East China Normal Univ., Shanghai, China; [2]Inst. of Brain Sci., [3]Fudan Univ., Shanghai, China; [4]Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Axo-axonic cells (AACs; also called Chandelier cells) is a specialized GABAergic interneuron (IN) subtype that selectively innervates pyramidal neurons (PyNs) at the axon initial segment (AIS) and veto action potential initiation. AAC was previously found in the cerebral cortex, hippocampus and amygdala, recently reported in all the pallium-derived brain structures. However, AAC in the lateral and basal nucleus of the amygdala, exceptional characterization and specificity, as well as its contributions in cued threat conditioning has not been well defined. Here we used a combination of neuroanatomical tracing, light and electron microscopic investigation, fiber photometry, functional manipulations and electrophysiology to characterize a previously unknown interneuron in the basolateral amygdala (BLA). We achieved cell-type-specific genetic manipulation and found that activation of AAC^{BLA} mitigates overall proactive defensive behaviors during US and CS, whereas activation of PyN^{BLA} provoke AAC^{BLA} inhibition. We report that the AAC^{BLA} controlling the firing of PyNs play an indispensable role in axo-axonic inhibition in the amygdala network. Functional manipulations revealed that the AAC^{BLA} is necessary and sufficient for acquisition, consolidation and expression of learned threat measured with freezing. These findings extend our understanding of the scope and nature function of AAC specific contributions to learning, and maybe a promising therapeutic target for treating pathological fear and anxiety in post-traumatic stress and panic disorder.

Disclosures: Y. Zhou: None. **P. Ma:** None. **W. Qu:** None. **Z. He:** None. **M. Wu:** None. **M. He:** None. **Y. Tai:** None. **J. Lu:** None. **L. Lin:** None. **Y. Gu:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.03/G6

Topic: G.01. Fear and Aversive Learning and Memory

Title: Exploring Behavior in Habenular Prkar2a Deficient Mice in Aversive Paradigms

Authors: *E. R. LESKO[1], E. LONDON[3], N. EISEN[1,4,2], G. A. VARGISH[1], A. CACCAVANO[5], C. J. MCBAIN[6];
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Abstract: The protein kinase A regulatory subunit type II alpha (PKA RIIα) is ubiquitously expressed peripherally, but within the central nervous system is nearly exclusively expressed within the small epithalamic structure, the medial habenula. The medial habenula has been shown to modulate intrinsic motivation and aversive behavior as well as primary reinforcement, and voluntary activity. Previous findings from our lab indicate when the Prkar2a gene, coding for PKA RIIα, was globally removed (RIIαKO), there were significant differences in the mice's primary reinforcement and voluntary activity. Knockout mice consumed significantly less of a chronic high fat high sugar diet and exercised more than their wildtype (WT) counterparts. Due to significant differences in appetitive behaviors we hypothesized differences in behavioral responses to aversive stimuli. To test this, we used three aversive paradigms starting with the least averse (bitter taste) and finishing with the most averse (opioid withdrawal conditioned place aversion). Interestingly, using a one-bottle (no choice) paradigm there were no differences in consumption of quinine (100µM - 2,000µM) compared to water. This led us to believe the mice habituated to the bitter taste. Our next steps include a 2-bottle choice quinine/water paradigm on quinine naive mice. The next aversive paradigm we used was conditioned taste aversion by pairing 10% sucrose with lithium chloride injections to associate something hedonic with something aversive. Our analysis showed no difference between genotypes in the reduction of sucrose consumed after conditioning. The last paradigm, conditioned place aversion, was conducted by establishing opioid dependence and then eliciting withdrawal using naloxone hydrochloride and immediately confining the mice to a randomly assigned chamber with distinct visual context in a 3-chamber apparatus for 15 minutes. Male mice displayed acquisition of conditioned place aversion, and interestingly the rate of extinction was significantly faster in male KO mice indicating a decreased aversive response compared to WT. Our female mice didn’t display conditioned place aversion acquisition but did have significant differences in jumping behavior (a sign of withdrawal) with female KO exhibiting significantly less jumps than their WT counterpart. Indicating female KO had attenuated withdrawal response. This work adds insight into the role of PKA signaling in MHb regulation of aversion, specifically in the context of opioid withdrawal and associated aversive behavior.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.04/G7

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIDA Grant DA047678
NIDA Grant DA041482

Title: Investigating the behavior of visual looming stimuli-induced fear learning

Authors: *R. PAVCHINSKIY[1], T. G. FREELS[2], A. R. TAPPER[2];
[1]Univ. of Massachusetts Chan Med. Sch. Grad. Program in Neurosci., Worcester, MA;
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Abstract: Anxiety disorders affect ~31% of U.S. adults in their lifetime. Aberrant fear processing where non-fearful stimuli triggers fear behavior contributes to anxiety. Fear perception and response are critical behaviors driven by intrinsic neural networks. Elucidating potentially threatening stimuli as non-fearful triggers habituation to fear and is an imperative survival instinct. However, specific brain circuitry driving inhibitory learning of fear responses are not fully elucidated. Moreover, behavioral paradigms assessing fear learning without utilizing pain, i.e. foot shock, are underexplored. To assess behavioral habituation to psychological threat, we developed a multi-day visual looming stimulus (VLS) paradigm where mice receive 5 presentations of an overhead loom stimulus, mimicking a bird of prey, for 3 days. The looming apparatus contained a lowered shelter across from an overhead monitor which displayed the looming stimulus, consisting of 15 repetitions of an expanding circle (250 ms expansion, 250 ms hold, and 500 ms pause per repetition). In response to the first looming trial, we observed multiple fear associated behaviors including freezing, fleeing, and tail rattling. Mice displayed robust freezing during the initial looming trial which significantly decreased, eventually returning near pre-loom baseline by the third day. Time spent in shelter following stimulus presentation decreased on the second and third day when compared to Day 1. Interestingly, tail rattle responses were abolished following Day 1 of the VLS paradigm. More detailed analysis within Day 1 looming revealed a behavioral shift from freeze to delayed flee between the first and fifth trial of Day 1 VLS marking a shift in threat perception. Together, these results establish multi-day VLS as a non-Pavlovian fear learning model to help identify novel neurocircuitry underlying inhibition of fear responses to naturalistic threats.

Disclosures: R. Pavchinskiy: None. **T.G. Freels:** None. **A.R. Tapper:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.05/G8

Topic: G.01. Fear and Aversive Learning and Memory

Title: The influence of classical music on fear memory recall

Authors: *L. CAVALCANTE[1], D. JÚNIOR[1], M. SILVA PRADO[1], G. GERMINIANI[1], C. SARTORI[2], R. S. DE FARIA[3];
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Abstract: The preservation of fear memory is integral to adaptive survival mechanisms, whereas its attenuation is pivotal in mitigating the development of phobias and post-traumatic stress disorder. Despite the established efficacy of music therapy in augmenting memory consolidation, our inquiry scrutinizes its potential impact on fear memory retrieval. To this end, we utilized 12 female C57/BL6 mice, randomly assigned to two groups: G1 - Mozart (n = 6) and G2 - Control (n = 6). The former group received exposure to Mozart's Sonata K448 from 9 pm to 7 am, commencing from intrauterine life, whilst the latter group experienced only ambient sounds. To mitigate potential behavioral biases stemming from environmental novelty, following 50 days of music exposure, the mice underwent a 4-day habituation phase. On the 55th day, aversive conditioning ensued, wherein G1 mice received paw shocks concurrently with a sound stimulus. Subsequently, on the 81st day, a recall test was administered, repositioning the animals within the training apparatus devoid of any stimuli presentation. Procedures were meticulously recorded and archived for subsequent analysis, employing freezing behavior as an index of fear memory. Statistical significance, denoted by a mean standard error of freezing time at $p \leq 0.050$, underscored pertinent findings. Notably, during the recall assessment, discernible disparities emerged in freezing durations between the Mozart and Control cohorts ($p=0.047$). Consequently, our findings substantiate that female mice exposed to Mozart's Sonata K448 exhibited prolonged freezing responses compared to their control counterparts, indicative of a positive influence of music on fear memory retrieval. Accordingly, we posit that the Mozart effect potentiates the recollection of aversive memories, thereby engendering enduring mnemonic traces.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

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Program #/Poster #: PSTR126.06/G9

Topic: G.01. Fear and Aversive Learning and Memory

Support: NINDS Grant T32NS105602
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Internal funding from the UW-Madison School of Medicine and Public Health

Title: Modulation of threat assessment by psilocybin and DMT

Authors: *J. RAZIDLO[1], N. JONES[2], C. J. WENTHUR[3];
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Abstract: Psychiatric disorders such as Major Depressive Disorder (MDD) have become an increasingly prevalent issue and are compounded by the limited efficacy of current treatment options. To combat these disorders, researchers have focused on novel therapeutic approaches. Two promising treatments are the serotonergic 5HT2A agonists and classical psychedelics, psilocybin and N,N-dimethyltryptamine (DMT). These compounds have been shown to exert rapid antidepressant effects through mechanisms that have yet to be fully understood. It has been proposed that the therapeutic mechanism of these drugs is their rapidly induced, transient window of neuroplasticity after administration. Impaired plasticity is observed in patients with MDD, and individuals have reported decreased depressive symptoms after taking psychedelics. These improvements in mood have been reported to last weeks to months. Despite this, there are no studies to date that assess the duration of this critical window. To study this window of plasticity at the behavioral level, we used C57BL/6J mice and the associative learning task of fear conditioning (FC). Mice were administered a single intraperitoneal (IP) injection of saline, psilocybin (3 mg/kg), or DMT (10mg/kg) prior to behavioral testing. Limited behavioral differences were seen between animals treated with psilocybin compared to controls. Strikingly, extinction learning was severely impaired in animals that received DMT compared to control animals. This behavior was carried over to the following day, where animals that received DMT showed enhanced fear renewal compared to controls. Further research is needed to understand any sex dependent effects of psychedelics, as well as dose and timing of drug administration.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.07/G10

Topic: G.01. Fear and Aversive Learning and Memory

Support: PID2019-110739GB-I00 (Ministerio de Ciencia, Innovación y Universidades, FEDER, UE)

Title: Modulation of fear conditioning by chronic methylphenidate exposure during adolescence

Authors: *R. MARTINEZ MARIN[1], K.-Y. TSENG[2], F. MONTIEL[1], J. LOPEZ[1], J. VARGAS[1], E. DÍAZ ARGANDOÑA[1];
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Abstract: Methylphenidate (MPH) is a widely used psychostimulant to treat Attention Deficit Hyperactivity Disorder in both adolescents and adults. Specifically, it is theorized that the use of psychoactive substances during adolescence may lead to atypical development of behavioral responses that endures through adulthood, many of which are dependent on the maturation of corticolimbic circuits. Here we implemented a fear conditioning paradigm to examine how chronic oral MPH administration during adolescence (P42-63) impacts both the acquisition and its extinction in adulthood (P280-290). We found a treatment x sex interaction ($p<0.05$, 2-way ANOVA) with female MPH-exposed rats exhibiting a deficit in fear extinction when compared to female saline controls, while both MPH- and saline-exposed male rats showed comparable level of fear extinction. These findings show a differential impact of adolescent MPH exposure on fear processing in males and females, revealing the importance of considering sex-specific responses and long-term effects when evaluating psychostimulant interventions.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.08/G11

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant (RO1NS106915)
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Title: Predator odor stress reduces endocannabinoid signaling and enhances subsequent fear memory

Authors: *M. SAYED[1,2], C. J. DUBOIS[1], J. FAWCTT-PATEL[1,2], M. A. FAROOQ[1,2], J. LIU[1,2];
[1]LSU Hlth. Sci. Ctr. Cell Biol. & Anat., New Orleans, LA, LA; [2]Southeast Louisiana VA Healthcare System, New Orleans, LA

Abstract: The cerebellum has emerged as a key player in cognition and emotion. Our lab previously showed that fear conditioning increases the level of monoacylglycerol lipase

(MAGL), which accelerates the degradation of 2-arachidonoylglycerol (2-AG), the major endocannabinoid (eCB) in the cerebellum. This results in a reduction in cerebellar eCB levels and is required for fear memory formation. Since stress is known to enhance fear memory, we hypothesized that a stress-induced reduction in endocannabinoid levels would increase subsequent fear memory formation. We quantified the cerebellar levels of diacylglycerol lipase (DAGL), a 2-AG production enzyme, using Western blotting. Three hours following fox urine exposure, we found that DAGL levels in cerebellar lobule 5/6 was decreased by 40% relative to naive mice. In contrast, the activity of MAGL, an enzyme that degrades 2-AG, remained unaltered. Therefore, predator odor stress reduced 2-AG levels by altering its synthesis, but not its degradation. We next determined the effect of this change on endocannabinoid signaling in cerebellar cortex. In naive mice, we found that bath application of the CB1 receptor (CB1R) antagonist NESS0327, increased the frequency of miniature inhibitory postsynaptic currents (mIPSCs) in cerebellar molecular layer interneurons, indicating the presence of a tonic eCB signal. However, after exposure to predator odor, NESS0327 failed to alter mIPSC frequency, suggesting a decrease in tonic eCB signaling. This reduction was not due to a decline in CB1 receptor signaling as the CB1R agonist WIN55212-2, reduced the frequency of mIPSCs in molecular layer interneurons of stressed mice by approximately 30%, which is similar to the effect seen in naive animals. If the loss of eCB signaling enhances fear memory formation, we predicted that a CB1R agonist would increase eCB signaling and prevent the enhancement of fear memory by stress. To test this idea, mice were exposed to predator odor for 5 minutes and then a fear conditioning paradigm 3 hours later. Next day, these animals exhibited a significantly higher freezing response to tone during the memory retention test compared to mice subjected to fear conditioning alone. Administration of the CB1R agonist ACEA (i.p.) after stress prevented the enhancement of fear memory. Therefore, a stress-induced decrease in eCB signaling can promote subsequent fear memory formation.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

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Topic: G.01. Fear and Aversive Learning and Memory

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Title: Hypothalamic control of acquisition of learned flight induced by threat imminence

Authors: *A. TOROSSIAN[1], B. MIRANDA[1], F. M. REIS[1], E. HILGERT[1], R. GUDIPATI[1], W. WANG[1], P. J. SCHUETTE[1], A. ADHIKARI[2];
[1]UCLA, Los Angeles, CA; [2]Dept. of Psychology, UCLA, Los Angeles, CA

Abstract: The neural circuitry of threat-induced defense has been studied extensively with fear-conditioned responses like freezing. Escape, however, has mostly been studied in situations with innate threats, though it can also be a flexible experience-dependent learned process with high adaptive value. Naturalistic escape in rodents is usually elicited by a chasing threat such as a predator, but this process is difficult to simulate in a lab. Here, we developed a novel fear conditioning assay in which mice learn to escape from a moving shock grid. The moving shock grid simulates aspects of predatory chase. In this assay, mice of both sexes rapidly learn 'flight upon grid approach' (FUGA). We reasoned that circuits known to be involved in escape and learned defensive actions may be involved in FUGA acquisition. Fittingly, cholecystokinin (cck)-expressing cells in the hypothalamic dorsal premammillary nucleus (PMd) are necessary for escape from innate threats and the PMd is involved in conditioned avoidance of predator odor. Together, these findings suggest that the PMd may be involved in FUGA acquisition. To test this, we chemogenetically inhibited the PMd-cck cells during fear acquisition of FUGA. We found that PMd-cck inhibition during acquisition disrupted the display of FUGA during fear retrieval. PMd-cck inhibition during fear acquisition reduced the number and speed of successful FUGA responses during retrieval compared to controls. To test the role of motion and threat imminence in the PMd's ability to generate conditioned flight, we chemogenetically inhibited PMd-cck neurons during acquisition of contextual fear to a non-moving, stationary shock grid, and found no differences between groups. These data suggest the PMd is not required for conditioned avoidance of a stationary threat, but it is necessary for conditioned flight induced by moving/chasing threats. We are currently recording PMd-cck activity using fiber photometry to understand how its activity reflects this learning process. We will also chemogenetically inhibit PMd-cck cells during acquisition of tone-shock pairings in classical auditory fear conditioning to understand the extent of the PMd's role in cue-fear learning. These data show that the PMd is critical for acquiring learned escape from moving threats and underscore recent views demonstrating that the hypothalamus can have key contributions for learning flexible experience-dependent survival actions.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

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Topic: G.01. Fear and Aversive Learning and Memory

Support: VA Grant I01 BX006434-01

Title: Optogenetic manipulation of cholinergic basal forebrain neurons disrupts defensive action selection and acetylcholine release dynamics quantification during flight conditioning

Authors: *D. S. HEREFORD[1], K. EVANS[2], J. P. FADOK[3];
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Abstract: Attending to stimuli that predict aversive outcomes is critical in determining defensive action selection, and maladaptive defensive responses can arise from misattribution of salience to innocuous stimuli. Salience driven attention is known to be influenced by activity in the basal forebrain (BF), specifically the substantia innominata (SI), and this region has previously demonstrated a direct effect on the strength of fear memory acquisition (Jiang et al., 2016). Cholinergic populations in the SI are known to project to the basolateral amygdala (BLA), a primary coordinator of defensive responses. It remains unknown what role this cholinergic pathway plays in salience assignment during acquisition of a conditioned fear response and how it modulates defensive action selection. Using the latest generation of Acetylcholine (Ach) biosensors we record in vivo Ach release in the BLA (N=6) during Serial Compound Stimulus (SCS) fear conditioning. SCS conditioning uses two distinct auditory stimuli (tone and white noise [WN]) presented sequentially and terminating with a 1s foot shock (0.9mA) and results in a unique defensive phenotype of freezing to the tone and flight to the WN. Comparing the integrated area under the traces obtained on day 2 of conditioning, Ach release was found to be higher during the WN epochs compared to the tone epochs, implicating Ach in coding increased salience to stimuli that better predict aversive outcomes. Next, we optogenetically inhibited (N=3) or excited (N=4) cholinergic neuron terminals in the BLA of ChAT-IRES-Cre mice during WN epochs on day 1 of SCS fear conditioning. When compared with control animals, inhibition of the cholinergic population lead to reduced flight to WN on conditioning day 2 (CD2). Conversely, excitation of this population lead to increased flight to WN on CD2. These findings indicate that bidirectional manipulation of cholinergic signaling leads to defensive behavior selection inconsistent with the salience of threat predictive cues. Our results support our hypothesis that cholinergic cells in the SI are active in response to stimuli predictive of imminent threat. Current studies involve classifying projection specific BF ◊ BLA cholinergic neuron activity using genetically encoded calcium dynamics of cholinergic terminals in the BLA using GCaMP8s.

Disclosures: D.S. Hereford: None. **K. Evans:** None. **J.P. Fadok:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

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United States Department of Defense

Title: Prefrontal effects of norepinephrine prediction errors

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Abstract: Individuals must learn to predict levels of threat in environments containing uncertainty to respond with appropriate defensive behaviors. Neuromodulators have been shown to represent components of predictive learning models such as prediction error. However, sensitive investigations of the role of norepinephrine (NE) have been limited by the lack of high-resolution measurements and manipulations of NE and its downstream effectors in aversive learning. To determine the role of NE in aversive learning, we measured and manipulated NE in mouse frontal cortex using optical methods. We found that NE release is consistent with a prediction error, and correspondingly evoked PFC NE release enhances aversive learning. However, several novel features of NE release could only be explained by a model incorporating temporal uncertainty. We tested this model by manipulating temporal uncertainty and found that cue-offset NE scales with the resolution of uncertainty provided by cue offset. Ongoing studies will determine how NE threat signals shape cortical encoding of threat using combined opto-stimulation of NE release and one and two-photon microendoscopic calcium imaging, as well as how second messengers downstream of neuromodulators support threat learning. Determining the neural components of threat computations will inform the molecular and cellular mechanisms of threat learning and the accurate temporal prediction of threat.

Disclosures: A. Basu: None. **J. Yang:** None. **A. Yu:** None. **J. Rondeau:** None. **J. Feng:** None. **T. Yokoyama:** None. **M. Sakamoto:** None. **Y. Li:** None. **A.P. Kaye:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.12/G15

Topic: G.01. Fear and Aversive Learning and Memory

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VA grant (BX003893)
National Institutes of Health Grant (RO1NS106915)

Title: Activation of cerebellar endocannabinoid signaling disrupts the reconsolidation of associative fear memory

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Abstract: The cerebellum plays a crucial role in the formation of associative fear memories. Our recent study revealed that fear conditioning reduced the level of an endocannabinoid, 2-Arachidonoylglycerol, in cerebellar lobules V/VI and this is required for memory consolidation. Once consolidated, associative memory can be modified, via a process called “reconsolidation”. When a learned memory is reactivated, it briefly becomes unstable and then restabilizes, allowing the memory to be strengthened or weakened. The cerebellum is also critical for memory reconsolidation as inhibition of protein synthesis in the cerebellar vermis during the reconsolidation period disrupts memory recall. Using a Pavlovian fear conditioning paradigm (FC), we now show that the activity of cerebellar Purkinje cells controls the reconsolidation of fear memory. We exposed male L7::Gq(+)-GqDREADD (Gq DREADD receptors selectively expressed in Purkinje cells) mice to a fear conditioning paradigm (tone + shock) followed by a reactivation stimulus (tone alone) in a novel context 10 days later. J60 (a DREADD receptor agonist) was then injected i.p. Three days after the reactivation of the fear memory, we assessed the retention of this fear memory. These mice displayed lower freezing responses to tone during the memory retention test, compared to saline injected controls. Thus in vivo pharmacogenetic activation of the GqDREADD pathway in Purkinje cells (PCs) disrupted fear memory reconsolidation. These effects were only observed in male L7::Gq(+)-DREADD mice, but not in females. Since activation of the GqDREADD in Purkinje cells is known to evoke 2-AG release, we tested whether endocannabinoid signaling is responsible for the impairment of reconsolidation. Male L7::Gq(+)-DREADD mice were exposed to fear conditioning and then a reactivation stimulus, and administered endocannabinoid inhibitor AM4113 (3mg/kg, a CB1R antagonist) immediately after memory reactivation, 30 mins prior to a J60 injection. These mice exhibited greater freezing responses to tones during the memory retention test, compared to the control group that received saline injection prior to J60. Thus inhibition of CB1Rs rescued the memory reconsolidation that was disrupted by GqDREADD activation in PCs. Therefore, our results indicate that pharmacological activation of endocannabinoid receptors in the cerebellum impairs the reconsolidation of fear memory in male mice.

Disclosures: G. Kogias: None. **J.S. Liu:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.13/G16

Topic: G.01. Fear and Aversive Learning and Memory

Support: FAPESP 2023/02122-8
CAPES-PROEX 001
FAPESP 2022/02986-0
CAPES 88887.714569/2022-00

Title: Involvement of mineralocorticoid receptors in the ventral tegmental area on the expression of conditioned and unconditioned fear responses

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Abstract: The hypothalamic-pituitary-adrenocortical (HPA) axis regulates the secretion of corticosteroids, such as corticosterone, in response to both innate and conditioned aversive stimuli. Corticosterone, in conjunction with other mediators, plays a pivotal role in coordinating diverse aspects of stress responses. The present study examines the impact of blocking mineralocorticoid receptors (MR) in the ventral tegmental area (VTA) on unconditioned and conditioned fear responses in male and female rats. The effects of intra-VTA administration of spironolactone (MR antagonist; doses of 0, 5, and 10 μg/0.2 μL) were evaluated using the elevated plus maze test (EPM) and a contextual conditioned fear protocol in 36 adult Wistar rats (14 males and 22 females; CEUA protocol 2425060423). On day 1, following spironolactone or vehicle administration in the VTA, animals underwent the EPM test. Day 2 commenced the contextual conditioned fear protocol with a training session with footshock presentations. On day 3, spironolactone or vehicle was administered into the VTA before the fear conditioning test session to assess the freezing response, followed by a retest on day 4, without drug administration. Statistical analysis included one- and two-way ANOVAs, with Tukey's post hoc test for significance ($p < 0.05$). Intra-VTA injections of spironolactone reduced the percentage of entries into the open arms of the EPM in females ($F_{2,19} = 5.29$; $p < 0.05$), indicating an influence on unconditioned fear. No significant effects were observed in males ($p > 0.05$). Intra-VTA spironolactone reduced freezing behavior during the contextual test and retest sessions only in males ($F_{2,11} = 7.55$, $p < 0.05$), suggesting an impact on conditioned fear. No significant drug effects were observed in females ($p > 0.05$). The results suggest that blocking MR in the VTA has a sex-dependent pro-aversive effect on unconditioned fear and an anti-aversive effect on conditioned fear.

Disclosures: L.M. Taguchi: None. **A.R. de Oliveira:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.14/G17

Topic: G.01. Fear and Aversive Learning and Memory

Support: Marie Skłodowska-Curie grant agreement No 956414

Title: Cerebellar neuronal activity during emotional control and the role of cerebellar-mpfc pathway in fear learning

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Abstract: Although cerebellum has traditionally been considered as a motor control structure, a growing body of evidence points to the cerebellum as a crucial component of the neural network that subserves emotionally related behaviors. In fact, anatomical studies in animal models and functional connectivity MRI studies in humans have shown that extensive interconnection exists between the cerebellum and important structures of the emotional control network, including prefrontal (PFC) and parietal cortices, hippocampus, amygdala and periaqueductal gray (PAG). Accordingly, accumulating evidence supports a critical role of the cerebellum in emotional associative learning, particularly in pavlovian fear conditioning, in humans as well as in rodents. Despite existing evidence supporting the role of the cerebellum in the emotional network, a comprehensive understanding of cerebellar neuronal activity during emotion control is lacking. In this project, we aim to elucidate the activity of cerebellar cortical neurons in lobule VI during fear conditioning in mice. In addition, we intend to investigate the contribution of the mPFC activity, and to explore the function of the cerebellar-mPFC pathway during fear learning. To this end, we use a head-mounted miniature microscope for recording cerebellar or mPFC activity during fear conditioning paradigm in freely behaving animals. We use genetically encoded fluorescent indicators, particularly calcium sensors such as GCaMP, to image neural dynamics, and genetically encoded designer receptors (DREADD) to transiently activate or inhibit small populations of cerebellar neurons during the task. The results of our work will further our knowledge on the role of the cerebellum in fear conditioning and it will provide new insights on the contribution of the cerebellar-mPFC pathway in fear learning behavior.

Disclosures: C. Ciapponi: None. **L. Mapelli:** None. **E. D'Angelo:** None.

Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.15/G18

Topic: G.01. Fear and Aversive Learning and Memory

Title: Ventral tegmental area glutamatergic inputs from the parabrachial nucleus regulate long-lasting fear memory

Authors: *R. I. OSNAYA[1], H.-L. WANG[2], S. ZHANG[3], J. TORIJA MAXIMO[4], *L. BING[1], Z. D. BRODNIK[5], S. HAHN[2], R. YE[1], M. F. MORALES[6];
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Abstract: The ventral tegmental area (VTA) is a midbrain structure that plays a role in reward processing. The VTA contains dopamine neurons intermingled with glutamate and GABA neurons that respond to reward and aversion. The VTA neurons establish synapses with inputs from several brain areas, including the parabrachial nucleus (PBN), which plays a role in both pain and aversion. Here, by a multidisciplinary approach we determined the extent to which PBN inputs to specific subclasses of VTA neurons play a role in aversion. By VTA injection of the retrograde track tracer fluorogold (FG), we observed FG-neurons in the lateral PBN. By phenotyping of PBN^{FG} neurons, we demonstrated that within the total population of FG neurons, ~94% co-expressed glutamate transporter 2 (VGluT2) indicating that PBN^{VGluT2} neurons provide a major input to VTA. We next injected AAV5-DIO-ChR2-eYFP virus into the PBN of VGluT2::cre mice, and implanted an optical fiber on the VTA of ChR2-eYFP mice to induce local release of glutamate. ChR2-eYFP mice were tested in a three-chamber apparatus in which they received optical stimulation when they entered the laser-paired chamber. We found that ChR2-eYFP mice avoided the laser-paired chamber during 4 days of optical stimulation sessions, as well as in subsequent days when mice were tested in the absence of optical stimulation (up to 7 weeks). Next, we injected the retrograde HSV-LS1L-GCaMP6s viral vector in the VTA of VGluT2::cre mice to express GCaMP6s in PBN^{VGluT2} neurons innervating the VTA and by fiber photometry we recorded calcium transients in response to innate and learned threats. We observed increases of calcium signals PBN^{VGluT2}-VTA neurons in response to the presence of a predator (rat) and a predator odor (trimethylthiazoline, TMT). Additionally, we recorded the activity of PBN^{VGluT2}-VTA neurons when mice were exposed to a cue predicting a shock, we found that $PBN^{VGluT2\text{-}VTA}$ neurons respond to the cue predicting a shock up to 4 weeks after the last training session. These findings indicate that $PBN^{VGluT2\text{-}VTA}$ pathway is involved in the response to innate aversive stimuli and long-lasting fear memory. This work was supported by NIDA/NIH.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

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Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH/MH127085 (to Z.F.)
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Title: Genetically distinct thalamoreticular subnetworks for emotional cognition

Authors: N. D. HARTLEY[1,2], **J. TIAN**[1,2], N. ROME[1,2], A. KROL[2], *Z. FU[1,2];
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Abstract: The thalamic reticular nucleus (TRN) plays critical roles in sensory processing, arousal, and attention, making is well poised to regulate cognition during emotionally salient contexts. However, the cellular and circuit elements mediating these diverse functions of cognition during emotional learning are not well understood. We previously identified two populations of genetically segregated TRN neurons that are characterized by their expression of the SPP1 and ECEL1 genes which differentially project to first order (FO) and higher order (HO) thalamic nuclei, respectively (Li et al., 2020). By further generating SPP1-Cre and ECEL1-Cre mouse lines, we were able to recently delineate the brain-wide circuit architecture and distinct physiological functions of the FO and HO thalamic subnetworks. Using these new Cre lines, we identify two previously uncharacterized limbic circuits consisting of the insular cortex (INS) and central amygdala (CeA) that demonstrate strong bias in input patterns to ECEL1 and SPP1 neurons, selectively project to the ventral shell of the TRN (vsTRN), and signal through different forms of neurotransmission and neuromodulation, respectively. To probe the functional roles of FO and HO subnetworks downstream of limbic inputs, we developed a discriminatory fear conditioning (DFC) procedure that measures multiple domains of emotional cognition within the same experiment and performed chemogenetic inhibition of ECEL1 and SPP1 neurons in the vsTRN. We found that SPP1 neuron inhibition impaired the acquisition of cued auditory fear memory, without impacting sensory discrimination or general contextual memory performance, suggesting vsTRN SPP1 neurons are necessary for maximal emotional learning. By contrast, ECEL1 neuron inhibition impaired the early phase of cued fear extinction, without impacting sensory discrimination or contextual memory performance, suggesting ECEL1 neurons may be required for emotional executive control during behavioral inhibition. These findings establish distinct new functional roles of genetically segregated vsTRN subnetworks in emotional learning and validate the use SPP1-Cre and ECEL1-Cre mouse lines for investigating the role of distinct thalamoreticular subnetworks in cognition.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

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Program #/Poster #: PSTR126.17/G20

Topic: G.01. Fear and Aversive Learning and Memory

Support: R15 MH129932-01

Title: Sex differences in elevating endocannabinoid signaling in hippocampal-dependent fear conditioning in adolescent rats

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Abstract: Sex differences in responses to chronic stress are implicated in the higher prevalence of major depression and PTSD in females. Evidence of sex differences in endocannabinoid (eCB) physiology suggests that eCB signaling contributes to sexual disparities in fear conditioning. In the present study, we assessed the effects of increasing hippocampal eCB levels on hippocampal-dependent contextual fear conditioning (CFC) in adolescent female and male Sprague-Dawley rats. Through inhibition of monoacylglycerol-lipase (MAGL), hippocampal levels of the eCB, 2-AG, were elevated either prior to acquisition or to memory recall of CFC. Female and male adolescent rats were surgically implanted with cannula targeted to the dorsal hippocampus. Following a one-week recovery period, animals were administered 0.5 µl (2 µg/ µl) JZL184, a MAGL inhibitor through the cannulas either prior to acquisition (Day 1) or memory recall (Day 2). All sample sizes were n= 6 or greater, the size needed for 80% statistical power. In males, administration of JZL184 on either day increased freezing behavior compared to vehicle injected males during memory recall (Day 2). In females. JLZ184 administration on either day decreased freezing during memory recall testing. Ongoing work is investigating the effects of elevating Anandamide on CFC. These findings have implications in the use of medical cannabinoid treatment of disorders such as PTSD, as well as recreational cannabis use in adolescent/young adult females.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

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Topic: G.01. Fear and Aversive Learning and Memory

Support: Italian Ministry of Foreign Affairs and International Cooperation, grant n. US23GR05
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Italian Ministry of University and Research, Grant n. 2022HY8KXW (PRIN 2022)

Title: Brain-wide activation analysis reveals strong sexual dimorphism in the evolution of fear memory

Authors: A. FRANCESCHINI[1], G. MAZZAMUTO[4], C. CHECCUCCI[5], L. CHICCHI[2], I. COSTANTINI[6], M. PASSANI[7], B. A. SILVA[8], F. S. PAVONE[9], ***L. SILVESTRI**[3]; [1]LENS, Univ. of Florence, Sesto Fiorentino, Italy; [2]Dept. of Physics and Astronomy, Univ. of Florence, Florence, Italy; [3]Univ. of Florence, Sesto Fiorentino, Italy; [4]CNR-INO and LENS, Sesto Fiorentino, Italy; [5]Dept. of Information Engin., Univ. of Floence, Florence, Italy; [6]Dept. of Biol., LENS - Univ. of Florence, Sesto Fiorentino, Italy; [7]Universita' di Firenze, Firenze, Italy; [8]Inst. of Mol. and Cell. Pharmacol. (IPMC), Nice, France; [9]LENS, Sesto Fiorentino, Italy

Abstract: Fear responses are functionally adaptive behaviors that are strengthened as memories. Indeed, detailed knowledge of the neural circuitry modulating fear memory could be the turning point for the comprehension of this emotion and its pathological states. A comprehensive understanding of the circuits mediating memory encoding, consolidation, and retrieval presents the fundamental technological challenge of analyzing activity in the entire brain with single-neuron resolution. In this context, we develop the brain-wide neuron quantification toolkit (BRANT) for mapping whole-brain neuronal activation at micron-scale resolution, combining tissue clearing, high-resolution light-sheet microscopy, and automated image analysis. The robustness and scalability of this method allow us to quantify the evolution of activity patterns across multiple phases of memory in mice. This approach highlights a strong sexual dimorphism in recruited circuits, which has no counterpart in the behavior. The methodology presented here paves the way for a comprehensive characterization of the evolution of fear memory.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

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Program #/Poster #: PSTR126.19/G22

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIMH R21MH114182
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PSC-CUNY Awards

Title: Sex Differences in Serotonin Signaling in the Bed Nucleus of the Stria Terminalis

Authors: *J. LEE[1,2], R. RAVENELLE[3], J. LIU[4], N. S. BURGHARDT[5,2];
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Abstract: It is widely documented that women are more likely than men to develop post-traumatic stress disorder (PTSD), a disorder characterized by intense fear memory formation. Accumulating evidence implicates the involvement of serotonin in the extended amygdala in circuits underlying fear learning. Our lab has recently shown that optogenetically increasing serotonin in the bed nucleus of the stria terminalis (BNST) promotes fear learning in females only. However, it is not known if serotonin signaling in the BNST naturally differs between the sexes. We began exploring this possibility by investigating whether there is a sex difference in the density of serotonergic projections from the raphe nuclei to the BNST. Serotonergic neurons were labeled with the retrograde tracer cholera toxin subunit B (CTB), which was injected (0.25uL) into the right anterior dorsal BNST (adBNST) of transgenic mice expressing yellow fluorescent protein in serotonergic neurons (TpH2-ChR2-EYFP-Bac mouse line). We detected no differences between males (n = 6) and females (n = 7) in the average number of labeled cells in the dorsal (female = 5.52 cells/ mm^2; male = 5.81 cells/ mm^2) or median raphe nuclei (female = 3.99 cells/ mm^2; male = 2.98 cells/ mm^2). We then investigated whether there is a sex difference in the activation of these serotonergic projections during auditory fear conditioning. Mice were fear conditioned with 5 tones (2kHz, 80dB, 30 sec) that co-terminated with a foot shock (0.7mA, 2 sec) and perfused 90 minutes later for c-Fos immunostaining. As expected, fear conditioning increased the activity of serotonergic projections from the raphe nuclei to the adBNST (c-Fos+/EYFP+/CTB+ cells in naïve vs. trained mice, $p<0.01$), but our preliminary data revealed no sex difference in this effect (n=3-4/sex). Next, we used qRT-PCR to measure the expression of serotonin receptors (5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, and 5-HT7) in the adBNST of males and females. We found that transcript levels were the highest for 5-HT1A (*Htr1a*) and 5-HT2C receptors (*Htr2C*) in both sexes, but the relative expression of *Htr2C to Htr1a* was higher in females than males ($p < 0.05$). Interestingly, pharmacologically blocking 5-HT2C receptors with a local infusion of a 5-HT2C receptor antagonist (RS102221) into the adBNST did not affect acquisition or retrieval of a conditioned fear memory in females, but impaired within-session extinction in males (n=6-9/group). This work contributes to our understanding of the BNST as a sexually dimorphic brain region and demonstrates that there are differences between males and females in how serotonin signaling within this area mediates fear learning.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.20/G23

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01MH123768

Title: Neural circuits underlying estrous cycle state-dependent modulation of emotional memory

Authors: *N. E. BAUMGARTNER[1,2], K. ADCOCK BINION[2], G. C. BELL[2], N. S. DECHACHUTINAN[1], D. S. RUSSELL[1], A. DAHLEN[1], G. NEWBERRY[1], T. RUMBELL[3], J. SIMON[4], E. K. LUCAS[1,2];
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Abstract: Women are twice as likely as men to experience post-traumatic stress disorder (PTSD) and among people diagnosed, women report more severe and longer-lasting symptoms. These differences are partially explained by cycling ovarian hormones across the menstrual cycle, as low levels of ovarian hormones are associated with worsened PTSD symptoms including dysregulated emotional memory. Here, we tested the hypothesis that ovarian hormone fluctuations across the reproductive cycle contribute to state-dependent learning, a phenomenon in which memory encoding and recall occur most efficiently in the same physiological state. Using cued threat conditioning, the most well-established model of emotional memory, we compared male mice to female mice that underwent training and recall under the same or opposite ovarian hormone state. We targeted high (proestrus, P) and low (diestrus, D) hormone states for a total of 5 experimental groups: male, P>P, P>D, D>D, D>P. Cued memory recall was indistinguishable between males and P>P females. Remarkably, all other groups exhibited increased recall. Next, we investigated brain regions involved in these behavior effects using c-fos expression as a neural activity marker following threat conditioning in males and females in P or D. Analysis of 114 brain regions revealed hormone state-dependent activation in a limited number of regions. The most prominent differences were observed in robust engagement of the rostral lateral septum (LS)—a region not historically considered necessary for cued threat memory—specifically in P females. Next, we quantified c-fos reactivation in the LS following cued recall. Remarkably, we found enhanced state-dependent reengagement of the LS in P>P females. We next sought to identify cellular populations within the LS involved in this neuronal ensemble. We performed single nucleus sequencing of the LS in naïve and trained P females and identified 52 transcriptionally distinct cellular clusters. Of these, only two neuronal clusters exhibited immediate early gene activation in response to threat conditioning: one population expressing both somatostatin and neurotensin (SST-NTS), and the other expressing corticotropin-releasing hormone receptor 2 (Crhr2). Subsequent fluorescent in situ hybridization revealed hormone state-dependent engagement of LS SST-NTS, but not Crhr2 neurons, following threat conditioning in P females. Future directions will investigate the necessity and sufficiency of LS SST-NTS neurons in regulating these behavioral effects. Together, we report a crucial role of ovarian hormone states in modulating emotional memory via novel female-specific brain circuitry.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

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Program #/Poster #: PSTR126.21/G24

Topic: G.01. Fear and Aversive Learning and Memory

Support: P60: 46-948-32-C004 (2P60AA007611-36)
U24: 56-811-30 (AA029970-03)

Title: Dopaminergic Modulation of Basolateral Amygdala States and Its Implications for Anxiety and PTSD

Authors: *A. KUZNETSOV;
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Abstract: The basolateral amygdala (BLA) is central to emotional processing, fear learning, and memory. Dopamine (DA) significantly influences BLA function, yet its precise effects are complex. We present a mathematical model exploring how DA modulation of BLA activity depends on the network's current state. Specifically, we model the firing rates of interconnected neural groups in the BLA and their responses to external stimuli and DA modulation. BLA projection neurons are separated into two groups according to their responses - fear and safety. These groups are connected by mutual inhibition though interneurons. We contrast 'differentiated' BLA states, where fear and safety projection neurons exhibit distinct activity levels, with 'non-differentiated' states. We posit that differentiated states support selective responses and short-term emotional memory. On the other hand, non-differentiated states represent either the case in which BLA is disengaged, or the activation of the fear and safety neurons is at a similar moderate or high level. We show that, while DA further disengages BLA in the low activity state, it destabilizes the moderate activity non-differentiated BLA state. We show that in the latter non-differentiated state the BLA is hypersensitive, and the polarity of its responses (fear or safety) to salient stimuli is highly random. We hypothesize that this non-differentiated state is related to anxiety and Post-Traumatic Stress Disorder (PTSD).

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.22/G25

Topic: F.01. Neuroethology

Support: BT/HRD-NBA-NWB/38/2019-20(Y1)

Title: Eavesdropping on worms for science and investigation of memory transfer from one worm to another

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Abstract: Native preference and behaviour in organisms can be modified by learning and retained through the formation of memory. *Caenorhabditis elegans* has been proven to be an extremely important model system to study behavioural plasticity. In this study, we have looked at long-term associative memory (LTAM) in *C. elegans* by training them using two cues - the native chemoattractant isoamyl alcohol (IAA) and heat as the repulsive cue. This training method results in LTAM formation, observed in the form of loss of attraction from IAA due to aversive learning, lasting for up to 24 hours. Here we report that during training, *C. elegans* release some factors onto the plate that can act as signalling molecules necessary for LTAM. Removal of worms from these plates causes them to lose this memory despite undergoing aversive training. These molecules can in turn be taken up by naive and other known memory-defective mutant worms that have not undergone training, inducing aversive learning in these worms. We have performed RNA sequencing to look at differential gene expression in different conditions to investigate the underlying molecular pathway. Additionally, to identify the externally released factors, we have performed liquid chromatography mass spectroscopy (LC-MS) from the plates worms were trained on. Here we propose a mechanism by which *C. elegans* as a result of aversive training with IAA and heat, release some factors onto the plate through environmentally released extracellular vesicles (EVs), which can further be taken up by any untrained worm (naive or memory-defective mutants) and induce aversive learning in these worms without undergoing any prior training. In this study, we report that memory can be transferred from one worm to another, paving a new avenue of communication and signalling in *C. elegans*.

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Poster

PSTR126: Aversive Memory: Acquisition, Modification, and Expression

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR126.23/G26

Topic: G.01. Fear and Aversive Learning and Memory

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Title: Contribution of neuronal inflammatory pathways to the formation of perineuronal nets

Authors: *A. CICVARIC[1], E. M. WOOD[1], V. JOVASEVIC[2], H. ZHANG[1], Z. PETROVIC[1], A. CARBONCINO[1], K. K. PARKER[1], T. E. BASSETT[1], F. SANANBENESI[3], X. ZHANG[1], A. FISCHER[4], J. M. RADULOVIC[1,2,5];
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Abstract: A growing number of recent research underscores the vital role of perineuronal nets (PNN), specialized extracellular matrix structures surrounding neurons, in long-term memory storage via the stabilization of memory circuits. Despite the composition and cell specificity of PNN being well known, how PNN are generated and regulated in response to memory formation is largely unknown. We demonstrated previously that memory formation renders gene expression in hippocampal neurons active over 20 days. At 96 h, the majority of differentially expressed genes were genes involved in the inflammatory responses (TLR9, RELA, IFNAR1), while at 21 days, there was a significant upregulation of the cilum- and extracellularmatrix-associated genes. Moreover, depletion of hippocampal primary cilium inhibited remote memory retrieval accompanied by the absence of PNN. These results indicated a pivotal role of primary cilium in long-term memory persistence and PNN organization and stability. Here, we used genetic and immunohistochemical approaches to study whether the neuronal inflammatory pathways TLR9, RELA, and IFNAR1 directly contribute to ciliogenesis and PNN build-up following CFC. We showed that depletion of TLR9 impaired ciliogenesis and PNN build-up. These effects were replicated in the mice lacking RELA but not IFNAR1, indicating that RELA is the likely effector pathway downstream of Tlr9. Collectively these data demonstrate a molecular and cellular mechanism by which inflammatory signaling in hippocampal neurons subserve the formation of long-term memory.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.01/G27

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Plasticity in Intratelencephalic Neurons in the Dorsomedial Prefrontal Cortex is Necessary for Goal-Directed Learning

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Abstract: Goal-directed behavior refers to the purposeful performance of an action aimed at achieving a desired outcome. While previous studies have highlighted the importance of the dorsomedial prefrontal cortex (dmPFC) in facilitating goal-directed learning, the specific neuronal cell types necessary to drive this learning remain unexplored. Within the dmPFC, both intratelencephalic (IT) and pyramidal tract (PT) neurons project to various brain regions. Notably, IT neurons in the dmPFC send bilateral projections to the dorsomedial striatum (DMS), forming a critical circuit implicated in goal-directed learning. The current research utilizes a transgenic approach to selectively target the IT and PT neuronal population in the dmPFC in goal-directed learning. Initially, it was observed that in an IT-specific Cre-driver mouse line, Cre-expressing IT neurons exhibited dense bilateral innervation in the dorsal striatum. Subsequent instrumental training, relative to yoked training, led to time-dependent and laminar-specific increases in elevated extracellular signal-related kinase phosphorylation (pERK) signalling in IT neurons, with immediate increases in layer 2/3 IT neurons, followed by layer 5/6 IT neurons one-hour post-training. Moreover, associated with this ERK plasticity, alternations in inhibitory and excitatory synaptic input onto layer 5/6 IT neurons persisted for at least four hours after training, as the balance of input was shifted to favor excitation. Pharmacogenetic inhibition of dmPFC IT neurons was found to abolish action-outcome learning, highlighting their necessity in the acquisition of goal-directed associations. Conversely, chemogenetic inhibition of dmPFC PT neurons in a PT-specific Cre-driver mouse line did not affect the acquisition of goal-directed associations or action-outcome learning. These findings collectively underscore the role of dmPFC IT neurons in mediating functionally relevant synaptic plasticity changes during the acquisition of action-outcome associations in goal-directed learning.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.02/G28

Topic: G.02. Reward and Appetitive Learning and Memory

Support: BRAIN initiative grant R01MH117040
Takeda Science Foundation Overseas Research Fellowship
Brain and Behavior Research Foundation #28979

Title: Brain-wide mechanisms of learning context in non-human primates.

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Abstract: Organisms flexibly adjust their behaviors depending on their environmental context. This ability is vital to survival in an uncertain world, and its malfunction can be catastrophic such as in gambling disorder. The ventrolateral portion of prefrontal cortex (vlPFC) has been implicated in both learning and probabilistic decision-making. What remains unknown is how the learning context influences the role of this area and interconnected parts of the brain in probabilistic decision-making. To address these issues, we conducted whole-brain functional imaging in rhesus macaques (N = 4) while they performed a probabilistic learning task. On each trial, animals chose between two visual stimuli that were associated with the reward probability of 0.9, 0.5, or 0.3. To assess the impact of learning context, subjects completed blocks of 100 trials with either novel visual stimuli (novel block) or stimuli that they were highly familiar (familiar block). Behaviorally, the animals employed distinct strategies depending on the learning context of the block. They consistently adopted a win-stay-lose-switch (WSLS) strategy in familiar blocks. By contrast in novel blocks they gradually shifted their strategy from explorative random selection to WSLS. This pattern suggests that the animals adapted their behavioral strategy based on reward outcome and the learning context. At the neural level, vlPFC activity tracked outcome regardless of learning context but encoded behavioral strategy preferentially in the novel blocks, where new association learning was required. Functional connectivity between vlPFC and anterior cingulate cortex (ACC) was higher when the behavioral strategy was relevant to task performance. By contrast, vlPFC and mediodorsal thalamus (MD) functional connectivity was most closely related when animals repeated the same choice during learning irrespective of learning performance. Further, pharmacological challenge in another cohort of animals (N = 7) who participated in the same paradigm using selective dopamine receptor-antagonists revealed a critical role of dopamine D2 receptors, but not D1 receptors, in vlPFC activity and modulation of behavioral strategy exclusively when new association learning was required. In summary, vlPFC activity and functional connectivity with other brain areas are directly modulated by the learning context. Further, our data suggest a direct link between dopamine D2 receptors and the context-dependent role of vlPFC in learning. Such a role for D2-receptors may represent a potential neural mechanism underlying psychiatric disorders with aberrant or biased decision.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R00MH118422
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the Scott Alan Myers Endowed Professorship
NRF of Korea RS-2023-00242703

Title: Two distinct computational mechanisms underlying extinction learning

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Abstract: When a cue that once predicted rewards no longer does so, animals stop seeking rewards. While initial learning models (e.g., temporal difference reinforcement learning, TDRL) believed that such extinction is unlearning of the original association, extensive evidence shows that the original cue-reward memory is retained following extinction. For instance, when the cue-reward association is experimentally restored after extinction, animals reacquire the association much faster than during the initial acquisition, implying maintenance of a memory of the original association. The computational basis of this memory remains elusive. Within TDRL, one proposal for this memory is that the "value" of the cue (i.e., how many future rewards it predicts) is stored in memory conditional on an additional latent state that specifies whether the current context is extinction or conditioning. Thus, new memory of cue value at extinction does not erase the original memory of cue value at conditioning. However, how animals infer such latent states remains unclear. An alternative theory of associative learning, Adjusted Net Contingency of Relation (ANCCR), proposes a different computational mechanism for extinction. This model hypothesizes that animals first learn a retrospective association, $P_{cue<-reward}$, by retrospectively searching for a cause when they receive a meaningful stimulus like a reward. This retrospective association is then transformed into a prospective association using a Bayes' rule like computation, $P_{cue->reward} = P_{cue<-reward}*P_{reward}/P_{cue}$, which enables animals to predict future rewards and drive behavior. In the ANCCR framework, because updates to retrospective associations occur only when a meaningful stimulus is encountered, retrospective association remains intact in standard extinction paradigms where no reward is given. Rather, ANCCR explains behavior extinction in these paradigms as a result of reduction in overall reward rate, which suppresses prospective association. Thus, ANCCR predicts that the 'original memory' is stored as a form of retrospective association, and complete unlearning can only occur when the retrospective association is erased. Here, we test and find support for this prediction experimentally and with simulations.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

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Program #/Poster #: PSTR127.04/G30

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01AA029661

Title: Computational properties of alcohol memory in a Pavlovian conditioning paradigm

Authors: *F. FAROUQ[1], V. K. NAMBOODIRI[2], H. JEONG[2], A. SANDERS[3], G. NAIK[4], D. A. BURKE[2], N. BELUR[4];
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Abstract: Addiction is hard to treat because it is a chronic, relapsing disorder with memory of prior drug use being the primary driver of relapse. However, the nature of this long-term memory remains unknown. For instance, during abstinence, people with substance use disorder often experience prior drug-associated cues without drug use. Yet, the cue-drug memory remains intact in the brain despite this apparently weakened association. The reasons for such long-term maintenance of cue-drug memories remains unknown. We recently proposed a theory that such long-term memories reflect a retrospective association, i.e., how often cues precede drug use, and therefore can only be degraded by drug use in the absence of the cues. If this computational theory is correct, it will provide several hypotheses for management of these maladaptive memories. Here, we test this idea for a cue-alcohol memory. Specifically, we utilize alcohol as a reward in a head-fixed Pavlovian conditioning task for mice that have undergone a previous intermittent access two-bottle choice (IA2BC) procedure with 20%(v/v) alcohol. In this task, we investigate the process of extinction and retrospective associations through two ways: when animals that have learned the association between alcohol and a sound cue get no rewards at all during the extinction phase in group 1 (n=7), and, when animals that have a learned association get no rewards following any sound cue during the extinction phase but obtain random rewards in the intertrial interval in group 2 (n=7). We predict and find support for the hypothesis that the retrospective association strength will be much lower for the group that obtains random alcohol rewards, thereby decreasing the ability of the cue in driving rapid reacquisition of alcohol seeking. This decrease in retrospective association strength between cue and reward can have implications for not only addiction treatment, but also PTSD.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Program #/Poster #: PSTR127.05/G31

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01MH129582
R01AA029661

Title: Sex difference in alcohol valuation

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Abstract: Alcohol use disorder (AUD) is a chronic, relapsing neuropsychiatric disorder that is characterized by an initial escalation of alcohol consumption and repeated cycles of intoxication, withdrawal, and craving—the precise mechanisms for which remain unknown. To address this gap, we first developed a behavioral paradigm for voluntary alcohol consumption in head-fixed mice. Given the option to choose between water and 20% alcohol drops, both male and female mice readily consumed the 20% alcohol solution, demonstrating a moderate preference for 20% alcohol. This preference mirrored that observed in the intermittent access to 20% alcohol in a two-bottle choice paradigm conducted in the homecage, a well-established protocol used to induce high levels of alcohol consumption in freely moving mice. Next, to model the cue-alcohol memories elicited in cue-induced relapse, we developed a cue-alcohol Pavlovian learning task for head-fixed mice. Strikingly, only male mice show evidence of behavioral learning or immediate alcohol consumption after alcohol delivery. Female mice consume fewer rewards and with a longer delay following alcohol delivery. Additionally, lick rate during the consumption period is much lower in females than in males. Our findings suggest a shift in the value of the 20% alcohol solution in a context in which alcohol can be freely chosen compared to a context in which alcohol is unexpected, in female mice only. In other words, the subjective value of a reward can depend on whether animals initiate reward delivery, and this process can exhibit sex differences.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.06/G32

Topic: G.02. Reward and Appetitive Learning and Memory

Title: The Role of NACHO in Learning and Memory

Authors: *K. MARQUEZ[1], J. I. VIDES VENTURA[2], L.-B. SHINN[1], M. WU[3], W. JOINER[4], Y. SHERAFAT[5];
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Abstract: The Role of NACHO in Learning and Memory

Authors Karina Marquez B.A, Levi Shinn B.A, and Yasmine Sherafat Ph.D.

AbstractLearning and memory are essential tools for our survival and allows us to build our advancement based on previous experiences. During a learning experience, we collect new information based on current experiences and combine them with memories stored in the past. At the neurobiological level, memory depends on the increased activity and connections of neurons. The Novel Acetylcholine Receptor Chaperone (NACHO) is a chaperone protein located in the endoplasmic reticulum of neurons and is known to facilitate the trafficking and assembly of the nicotinic receptors. Nicotinic receptors within the hippocampus are known to enhance learning and memory abilities. In this study, we sought to examine the role of NACHO in learning and memory in mouse models. To do this, we surgically knocked down NACHO in the hippocampus of our experimental group and compared it to a control group. We then performed behavioral assessments such as the locomotion and the novel object recognition (NOR) procedure to examine how the knockdown of NACHO in the hippocampus impacted movement and learning and memory skills. Based on previous research we hypothesized that the mice who had NACHO knockdown within the dorsal hippocampus would exhibit no change in locomotor behavior and would spend less time with the novel object during the NOR procedure. Once we analyzed all data we found that NACHO knockdown mice were significantly less likely to recognize the novel object, exhibited more movement during locomotion and spent more time in the center compared to the mice in the control group. Based on our findings, NACHO plays a role enhancing learning and memory skills. Future therapeutics for Alzheimer's disease can aim to increase NACHO within the hippocampus.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Title: Trans-neuronal intracellular arrest is an overruling mechanism mediating learning in the striatum

Authors: *C. S. GOULTON, C. NOLAN, C. SHEN, M. MATAMALES, J. BERTRAN-GONZALEZ;
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Abstract: The two main populations of spiny projection neuron (D1- and D2-SPNs) are interspersed in similar proportions across the striatum. We recently challenged conventional views of striatal function by highlighting a major role in learning: we identified a novel modulatory interaction whereby D2-SPNs suppress plasticity in neighbouring D1-SPNs (D2-to-D1 transmodulation), a process that is critical for the updating of instrumental learning (Matamales *et al.*, 2020). Here, we hypothesised that this effect relies on trans-neuronal modulation of intracellular signals, is independent of movement-related corticostriatal transmission, and may play a role beyond learning updating. Using mice, we studied plasticity territoriality in the striatum by placing both neuron types in functional competition through pharmacological stimulation: injection of GBR12783 (DAT inhibitor) and raclopride (D2-antagonist) strongly promoted transcriptional activation in D1- and D2-SPNs, respectively. However, sequential administration of these drugs in either order blocked these responses in D1-SPNs. The absent transcriptional activation in D1-SPNs contrasted with the summated increase in striatal dopamine (DA) induced by both drugs, suggesting that DA peaks can be overruled by postsynaptic modulatory interactions established amongst SPNs. Yet, in D1-SPNs, DA elevations did translate into an increase in cAMP, suggesting that D2-to-D1 transmodulation can intercept ongoing PKA signalling within D1-SPNs. Notably, molecular states did not align with changes in calcium transients in D1- or D2-SPNs, which instead correlated loosely with overall locomotor activity. We evaluated the primary role of this molecular cross-talk in instrumental learning by functionally manipulating D1- and D2-SPNs during acquisition of an action-outcome (A→O) contingency. Genetic ablation of D1-SPNs in the dorsomedial striatum disrupted original A→O learning, an effect that was mimicked by pharmacologically enhancing D2-SPN function only during training. Altogether our results uncover a prioritised cellular mechanism by which D2-SPNs exert determining influence over D1-SPN plasticity to mediate associative learning—a process that runs parallel to behavioural performance-related activity and that can override direct DA input.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH grant R00MH118422
NIH grant R01MH129582
NSF Graduate Research Fellowship
UCSF Discovery Fellowship

Title: Mesolimbic dopamine ramps reflect environmental timescales

Authors: *J. R. FLOEDER[1], H. JEONG[1], A. MOHEBI[1,2], V. K. NAMBOODIRI[1];
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Abstract: Mesolimbic dopamine activity was thought to operate in discrete "phasic" or "tonic" modes. However, recent evidence reveals a "quasi-phasic" mode in which mesolimbic dopamine activity exhibits ramping dynamics. This discovery reignited debate surrounding theories of dopamine functioning, and there is still no clear understanding of why dopamine ramps appear only under some experimental conditions. To investigate the conditions necessary for dopamine ramps, we turned to our recent work proposing that dopamine represents the Adjusted Net Contingency for Causal Relations (ANCCR), a teaching signal for causal learning. ANCCR simulations revealed that ramping dopamine dynamics depend on the duration of a memory trace of past events (i.e., on the eligibility trace time constant). Specifically, we successfully simulated dopamine ramps only when the eligibility trace time constant was small relative to the trial period. Our theory posits that the inter-trial interval (ITI) is a key variable controlling the eligibility trace time constant, such that a short ITI would produce a small time constant and result in dopamine ramps. To experimentally test this prediction, we used dLight fiber photometry to measure dopamine release dynamics as mice engaged in auditory Pavlovian conditioning while varying the ITI. Consistent with our simulations, we observed dopamine ramps only under short ITI conditions with dynamic auditory cues, confirming the pivotal role of ITI in modulating dopamine dynamics. Furthermore, we found a per-trial correlation between ramp magnitude and previous ITI, underscoring the rapid adaptability of the eligibility trace time constant. Extending our findings to instrumental conditioning using a virtual reality navigation task, we reproduced the core finding from Pavlovian conditioning, only observing mesolimbic dopamine ramps during the short ITI condition. Our results offer a unified framework for understanding dopamine ramps, positing ITI as a key modulator of eligibility trace time constant. While consistent with ANCCR, these findings emphasize the need to consider task design when interpreting dopamine dynamics and may prompt further investigations into alternative theories of dopamine function. In conclusion, our study elucidates the underappreciated role of ITI in shaping mesolimbic dopamine activity, providing critical insights into the conditions under which dopamine ramps emerge.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R00MH118422
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NIH F32DA060044

Title: Reward timescale controls the rate of behavioral and dopaminergic learning

Authors: *D. A. BURKE[1], A. TAYLOR[1], H. JEONG[1], S. LEE[2], B. WU[1], J. R. FLOEDER[1], V. K. NAMBOODIRI[1];
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Abstract: Cue-reward associative learning is controlled in the brain by mesolimbic dopamine. It is widely believed that dopamine drives behavioral learning by conveying a reward prediction error (RPE) in accordance with temporal difference reinforcement learning (TDRL) algorithms. TDRL implementations are "trial-based"—learning progresses sequentially across individual cue-outcome experiences. Accordingly, a foundational assumption in this family of models is that the more cue-reward pairings one experiences, the more one learns the cue-reward association. In contrast, we show that a dopamine-based retrospective learning algorithm predicts that the amount of cue-reward learning per experience is proportional to the duration between rewards—a fundamentally "non-trial-based" learning mechanism. Consistent with this latter prediction, we demonstrate that in mice conditioned to associate an auditory cue with sucrose delivery the amount of behavioral and mesolimbic dopaminergic learning per experience (i.e. learning rate) is proportional to the duration between rewards. We find that this behavioral and dopaminergic learning rate scaling holds across a range of reward intervals. Through experiments in which the number of trials per session, time in context, or reward probability is varied, we confirm that the learning rate is set by the interval between rewards rather than experimental parameters that generally covary with reward rate. Due to this learning rate scaling, experiencing *n* times fewer cue-reward pairings over the same total time results in *n* times more learning per pairing—thereby providing a mechanism for few-shot learning from sparse rewards. These findings fundamentally change our understanding of the neural algorithms of associative learning.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Program #/Poster #: PSTR127.10/G36

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH NIDDK Grant R01DK085721

Title: Activation of Hippocampal-Thalamic-Prefrontal Circuitry for Contextual Processing During Habituation to Novelty

Authors: *Z. IRVING[1], E. GREINER[2], G. D. PETROVICH[3];
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Abstract: Novel foods and novel environments both impact consumption, but how they interact across habituation is poorly understood. Our prior work showed that rats consume overall less in a novel environment than a familiar one, and females habituated slower than males to eating in a novel context. We also established that a first exposure to a novel feeding environment recruited multiple forebrain areas, including four regions established in contextual processing: the CA1 subfield of the hippocampus, the prelimbic (PL) and infralimbic (ILA) areas of prefrontal cortex, and the nucleus reuniens (RE) of the thalamus. Here we tested if context familiarity impacts habituation to novel food and if the CA1-PL/ILA-RE circuitry is recruited during habituation. Adult male and female Long Evans rats (n=8/group) were food deprived for 20h prior to consumption of novel, palatable Test Diet pellets in either a familiar context, their home cage, or a novel context for 4 habituation sessions and 1 final test. Rats were perfused 90 minutes after the start of the test, and brain tissue was processed for analysis of Fos induction. During the final test, rats tested in the novel context consumed less than those tested in the familiar context ($p=0.02$), and females ate less than males ($p=0.08$). Fos induction was higher in all four regions analyzed in the novel compared to familiar context condition and in females compared to males, except in the CA1. In the CA1 there was a main effect of context ($p=0.005$) but not sex. In the RE there was an effect of context ($p=0.002$) and sex ($p=0.05$), but interaction did not reach significance ($p=0.062$). The ILA and PL had similar patterns, and in both regions, there was an effect of context (ILA: $p=0.014$; PL: $p=0.007$) and sex (ILA: $p=0.072$; PL: $p=0.025$), but no interactions. We also examined if Fos induction patterns correlate between these regions. Due to the sex effects in most regions analyzed, we ran correlations separately for each sex. There were more correlations in females than males in both contexts. In familiar context tested males, PL and RE were correlated ($p=0.048$), while in the novel context, PL and CA1 were moderately correlated ($p=0.061$). For females tested in the familiar context, ILA was correlated with the RE ($p=0.07$) and PL ($p<0.001$). For females tested in the novel context, ILA was correlated with the PL ($p=0.017$) and RE ($p=0.022$), CA1 was correlated with ILA ($p=0.059$) and PL ($p=0.068$), and PL was correlated with RE ($p=0.017$). Collectively, these results suggest that the CA1-PL/ILA-RE circuitry is important for contextual processing late in habituation and may function differently in males and females.

Disclosures: Z. Irving: None. **E. Greiner:** None. **G.D. Petrovich:** None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.11/G37

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Brain RF1NS128896
McCamish Chair

Title: Dopaminergic dynamics in reward adaptation: Insights from nucleus accumbens dLight recording

Authors: *N. H. CHANG[1], E. D. DIMWAMWA[1], D. A. WEISS[1], S. RUSSO[1], A. M. F. BORSA[1], E. ULUTAS[2], J. E. MARKOWITZ[2], C. WAIBLINGER[1], G. B. STANLEY[1]; [1]Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA; [2]Biomed. Engin., Georgia Technol. and Emory, Atlanta, GA

Abstract: In dynamic environments, animals constantly adapt their behaviors to optimize outcomes. In operant conditioning tasks such as go/no-go or lever pressing, mice demonstrate this adaptability by gradually refining their responses to sensory stimuli to maximize rewards. This adaptive behavior underscores the critical role of dopamine in modulating behavioral responses and shaping decision-making processes. Specifically, dopamine release in the basal ganglia is thought to facilitate these adaptive behaviors, enabling mice to optimize their actions based on feedback from previous trials. Despite the recognized role of dopamine, its specific contribution as a signal guiding such adaptive behaviors remains largely unexplored. Here, we utilized dLight1.1, a genetically encoded dopamine indicator, to monitor dopamine release within the nucleus accumbens core—a key area for associating reward with sensory stimuli—during sessions with repetitive water reward delivery at flexible intervals. To assess the impact of reward magnitude on dopaminergic signals, we systematically varied the size of water droplets across multiple sessions with naive, untrained mice. Our findings revealed a gradual decline in the peak amplitude of dopamine transients as mice approached satiation, with larger rewards producing a more pronounced decline. Control experiments suggested that the decline in dopamine activity could not be attributed to photobleaching. These results suggest that dopamine signals encode not only the immediate subjective reward value but also significantly contribute to the animals' adaptation to varying reward conditions. To further elucidate how dopamine signals facilitate adaptive behavioral strategies, we are currently conducting dLight recordings in mice as they learn a go/no-go tactile detection task with varied stimulus and reward contingencies. This ongoing research aims to deepen our understanding of dopamine's role in sensory and reward-based learning.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.12/H1

Topic: G.02. Reward and Appetitive Learning and Memory

Support: CIHR 20R77768
NSERC 20R76081

Title: The mesocortical dopamine system does not encode reward prediction errors

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Abstract: One of the most influential theories in neuroscience states that dopamine (DA) projections to the forebrain convey Reward Prediction Errors (RPEs) in the service of reinforcement learning. This theory has been validated through countless Pavlovian conditioning experiments involving the mesolimbic and to a lesser extent, the nigrostriatal DA pathways. While it is often assumed that the theory also holds for the mesocortical DA system, Seamans & Yang (2004) cited a variety of reasons why this is unlikely. However, it has not been possible to broach the issue experimentally because microdialysis was the only technique available to accurately measure cortical DA levels and it is too slow to track transient DA changes on Pavlovian conditioning tasks. Newly developed, fast and highly-sensitive fluorescent DA sensors have overcome these limitations thereby allowing us to return to the question of whether the mesocortical DA system carries RPEs. In the present study, an optic fiber was placed in rat medial frontal cortex (MFC) and Dlight2.1 or GrabDA3h was used to measure DA levels during a task where rats were presented with tones paired with either a rewarding outcome (food pellet), an aversive outcome (footshock), or a null outcome (no outcome) in separate blocks of trials. Results from both indicators showed DA levels increased equally on food and shock trials. While DA responses varied with changes in outcome magnitude (ie more/less food pellets or shorter/longer shocks), the correlations were not linear and the effect was greater on food trials. 'Dips' in DA, consistent with negative RPEs, were never observed. Omitting outcomes attenuated the outcome-locked increase in DA equally on food and shock trials. Swapping the food with a shock on food trials should have created very strong negative RPEs, but this only slightly accentuated the outcome-locked increases in DA. Swapping the shocks with food on shock trials had the opposite effect. Hence, the MFC DA system does not appear to encode signed RPEs, a conclusion which is consistent with the lack of effect of MFC DA manipulations on reinforcement learning tasks (Ellwood et al 2017).

Disclosures: J. Seamans: None. **E. Croy:** None. **I. Gallello:** None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

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Program #/Poster #: PSTR127.13/H2

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R01DA036534
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McKnight Brain Research Foundation
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Title: Investigating the functional role of ventral tegmental area dopamine neurons in decision making under risk of punishment

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Abstract: To elucidate the functional role of ventral tegmental area dopamine (VTA DA) neurons in decision making under risk of punishment, male and female tyrosine hydroxylase (TH)-Cre transgenic rats expressing Cre-dependent GCaMP were trained on an operant-based risky decision making task (RDT). In this task, rats made discrete lever selections between a small, “safe” food reward and a large food reward accompanied by ascending risk of mild footshock (0%, 25%, 75%). As such, outcomes of the risky lever could be divided into “Wins” and “Losses” depending on whether delivery of the large food reward (which was delivered on every trial) was accompanied by footshock (which was delivered probabilistically). *In vivo* fiber photometric recording of VTA DA neurons revealed a signed prediction error signal such that neuronal activity increased to risky Wins and decreased to risky Losses. When signal was further broken down into the three risk probabilities, VTA DA neuron activity was found to be greatest when risky Wins occurred at the highest risk probability and was lowest when Wins occurred when there was no risk of footshock. To investigate if this change in VTA dopamine neuron activity was causal to risky decision making, Cre-dependent halorhodopsin was expressed in dopamine neurons of another subset of TH-Cre rats such that delivery of laser light via chronically implanted optic fibers resulted in temporally-specific inhibition of VTA DA neurons. After stable RDT behavior was established, rats performed the task with laser light delivery on Win or Lose outcomes. Relative to baseline sessions, inhibition of VTA DA neurons during Wins or Losses reduced presses for the large, risky lever in the next immediate trial. These findings support a causal link between risky decision making and VTA DA neuron activity.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Program #/Poster #: PSTR127.14/H3

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSERC
FRQNT

Title: Does dopamine stimulation prompt reward learning by inducing a scalar value or a prediction error signal?

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Abstract: The discovery that midbrain dopamine (DA) transients can be mapped onto reward prediction errors (RPE) in temporal difference models (TDRL) is a pinnacle achievement of neuroscience. Putative causal evidence for the RPE hypothesis comes from studies showing that stimulation of DA neurons triggers learning under conditions where it should not occur1,2,3. However, such stimulation could drive learning not by producing an RPE directly, but by providing added reward value and thereby indirectly inducing an RPE. This added value could support new learning even under conditions when it may be insufficient to support instrumental action4. Thus, studies that have examined the effects on learning of either increasing or decreasing the activity of DA at the time of reward have failed to disentangle these possibilities. Critically, the RPE and value hypotheses make divergent predictions under conditions of consistent, steady DA stimulation across multiple phases of learning. If DA transients signal scalar value, such stimulation should set an equally steady value signal that, once expected, should fail to produce new learning. In contrast, if DA transients signal an RPE, then such stimulation should support new learning indefinitely. Here we formalized and tested these predictions. We developed two computational models grounded in temporal difference reinforcement learning (TDRL) that dissociate the role of DA as an RPE versus a scalar value signal. We validated our models by showing that they both predict learning (unblocking) when VTA DA stimulation occurs during expected reward delivery in a behavioural blocking design and confirmed this behaviourally. We then pitted these hypotheses against one another by delivering constant optogenetic stimulation at the time of a food reward across both phases of an appetitive blocking design. Our models confirmed that under such conditions the scalar value hypothesis predicts blocking while the RPE hypothesis predicts unblocking. The results aligned with the predictions of the RPE model. Our study highlights the intricate conceptual relation between RPE and scalar value, offers a formalization of how stimulation of VTA DA neurons may signal each of those processes, and advances our understanding of the mechanism whereby VTA dopamine stimulation drives learning.

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Poster

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Program #/Poster #: PSTR127.15/H4

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R00MH118422
R01MH129582

Title: Mesolimbic dopamine release violates temporal difference reward prediction errors even in Markovian environments

Authors: *J. DISANTO[1], C. KIRST[2], V. K. NAMBOODIRI[3];
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Abstract: Learning to associate predictive cues with future outcomes is vital for animals' ability to seek out food and avoid danger. This associative learning is mediated by the activity of midbrain dopamine neurons, and the prevailing hypothesis of dopamine's algorithmic role is formalized by the temporal difference reinforcement learning algorithm (TDRL). Dopamine cell firing is believed to encode a learning signal in this algorithm, the temporal difference reward prediction error (TD RPE). However, this model assumes that animals use a particular representation of the task whereby the events correspond to states of a discrete time Markov process. This foundational assumption has not been rigorously accounted for in experimental tests of the hypothesis that dopamine encodes TD RPE, leading to a conventional practice of fitting Markov processes onto task designs post-hoc in such a way that theorist-defined states have no direct one-to-one correspondence with the sensory events experienced by subjects. Thus to rigorously test this TDRL model, we designed a task in which the sensory events the animal experiences exactly correspond to the modeled states of a discrete time Markov process. We reasoned that by designing a task that explicitly fulfills the key assumption of TDRL, we could perform a rigorous test of the hypothesis that dopamine encodes TD RPE. In our task, head-fixed mice experienced a stochastic and continuous sequence of auditory tones and infrequent sucrose rewards that were stochastically generated by a discrete time Markov process. We recorded dopamine release in the nucleus accumbens core using dLight 1.3b as mice learned the task over 10 days. Mice demonstrated learning of the task structure through preferential anticipatory licking during auditory cues that were most predictive of reward. Dopamine release was compared with simulated TD RPE, and we found that when the task was fully learned, dopamine responses to many cue sequences were inconsistent with TD RPE. Most notably, at self-transitions, i.e. when a cue was repeated, dopamine responses were positive, while TDRL predicts that self-transitions must produce a negative TD RPE. We observed this sign mismatch between dopamine signal and expected TD RPE at many other transitions in the Markov chain, as well as quantitative differences in magnitudes at several other transitions which could not be explained by a search over parameter values. Thus, we conclude that when the key assumption of TDRL is rigorously met, namely when the animal's experience directly corresponds to the states of a Markov process, dopamine release is not consistent with TD RPE.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.16/H5

Topic: G.02. Reward and Appetitive Learning and Memory

Title: ANCCR revisited: a normative model of cause-effect learning through dopamine

Authors: *J. VASTOLA;
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Abstract: Midbrain dopaminergic neurons are canonically thought to encode reward prediction errors, and hence play a crucial role in a temporal difference learning algorithm that allows the brain to learn the value of different actions and environmental states. However, a number of recent experiments appear to be in conflict with this idea. A controversial alternative hypothesis proposed by Jeong et al., which they call the ANCCR model, posits instead that midbrain dopaminergic neurons play a specific role in a cause-effect learning algorithm. However, the theoretical basis of the ANCCR model is unclear, and it is also unclear to what extent its components are separately falsifiable. We developed a normative theory of cause-effect learning that bears on these questions, and implies that models like ANCCR have two dissociable components: (i) an online cause-effect learning algorithm, and (ii) a reinforcement learning algorithm for estimating prospective/retrospective value. In particular, the online cause-effect learning algorithm can be viewed as an approximate form of Bayesian inference over possible causal structures, and the reinforcement learning component can be viewed in terms of a certain temporal difference learning algorithm. Our theoretical framework suggests several interesting ways to generalize the ANCCR model, and makes specific predictions about how best to test each component.

Disclosures: J. Vastola: None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.17/H6

Topic: G.09. Drugs of Abuse and Addiction

Support: R00 45758

Title: The organophosphate pesticide chlorpyrifos disrupts cognitive performance in a go/no-go sucrose reward task

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Abstract: The organophosphate Chlorpyrifos (CPF) is a compound which has been classified to be a moderately toxic agent. As a pesticide that took off en masse since 1965, CPF was most notably used to treat 50 different species of nut, fruit, vegetable, and cereal crops. Despite evidence suggesting significant health risks, a federal ban on the usage of CPF did not occur until 2021, and the long-term effects of extended exposure remain unknown. Although biochemical studies on the effects of CPF are widespread, behavioral testing remains sparse and lacks depth; however, human studies implicate developmental CPF exposure is involved in cognitive deficits and the etiology of attention deficit hyperactivity disorder (ADHD). Here, we tested the effects of subthreshold (non-detectable in fetal tissue) exposure to CPF on rats during development and observed decision making and cognitive performance in a go/no-go sucrose reward task. Pregnant Sprague-Dawley rats were given 6mg/kg/day CPF or safflower oil vehicle administered on wafer cookies (readily eaten) daily during gestational day (GD) 6-20. Offspring were raised to adulthood (post-natal day 55) before CPF and vehicle rats were trained to first self-administer sucrose. Then, the rats would be trained to forgo trial learning, and to finally perform the go/no-go (GNG) rule acquisition. Results indicated that developmental CPF exposure negatively impacted cognitive performance in the GNG task, particularly in male offspring. Norepinephrine (NE) receptors and transporters are typically involved in decision making behavior and ADHD pathophysiology, including the GNG tasks. Therefore, we then tested male and female CPF-exposed rats for the therapeutic potential of NE receptor antagonists (α2; Yohimbine and β; Propranolol) or NET/DAT transport inhibitors (e.g. Methylphenidate) to attenuate CPF-induced dysfunction. The β-adrenergic antagonist Propranolol impaired performance in controls and diminished execution to a greater extent in CPF exposed rats. Exposed males initiated fewer 30-minute trials compared to the vehicle males across all dose ranges. Between both correct Go and No-Go trials, CPF males scored lower for each dose compared to males with the vehicle; the only caveat being the same number of correct no-go trials for both CPF and vehicle males in dosage of 5.0 Propranolol. Methylphenidate improved performance consistently in CPF male rats only, while disrupting performance of controls. Thus, CPF exposure may contribute to the etiology of ADHD-phenotypes, and effects to perturb cognitive performance may be more prevalent in male offspring.

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Poster

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Program #/Poster #: PSTR127.18/H7

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA051598
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NIH Grant DA041480

Title: Cocaine self-administration disrupts model-based mechanisms of state learning

Authors: *S. GROMAN[1], J. TAYLOR[2];
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Abstract: Chronic use of cocaine leads to impairments in the ability of individuals to adaptively adjust their choice behavior in dynamic environments. These drug-induced deficits have been proposed to be result of disruptions to the reinforcement-learning systems that enable behavior to be flexible and goal-directed. Direct evidence supporting this hypothesis has, however, been limited. Emerging theories have suggested that reversal learning likely requires learning from outcomes, states, and beliefs but how these learning processes may be disrupted in addicted states is not known. The current study first sought to understand the relationship between reversal-learning and computationally defined reinforcement-learning systems and then to use this information to investigate the behavioral mechanisms of drug-induced deficits in reversal learning. Adult, male Long Evans rats were trained to make choices in a three-choice, probabilistic reversal-learning task. Choice behavior was then assessed in a multi-stage decision-making task and model-free and model-based learning quantified. We found that reversal performance was associated with model-based, but not model-free, learning. A change-point analysis was then conducted to identify the trial in which rats detected the reversal (e.g., exploit-to-explore change point) and then when the newly highest reinforced option was identified (e.g., explore-to-exploit change point). Variation in model-based learning was correlated with the exploit-to-explore change point whereas variation in model-free learning was correlated with the explore-to-exploit change point. These data suggest that different reinforcement learning systems play distinct roles in mediating state transitions. We then conducted a change point analysis of previously collected data in rats that had cocaine-induced reversal learning deficits. We found that the exploit-to-explore change point, but not the explore-to-exploit change point, was elevated in cocaine-exposed rats indicating that cocaine-induced reversal learning deficits are due specifically to disruptions in model-based learning of states. Future studies integrating *in vivo* imaging could provide key insights into the neural mechanisms that mediate these distinct mechanisms in normal and addicted states.

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Poster

PSTR127: Reinforcement, Learning, and Motivation

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.19/H8

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA IRP

Title: In search of neuronal ensembles that encode volitional social learning in mice

Authors: *L. RAMSEY[1], S. LEE[1], M. VENNIRO[2], Y. SHAHAM[3], B. T. HOPE[4];
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Abstract: Background: We recently developed a mouse model of operant social self-administration and choice (Ramsey et al. Biol Psychiatry, 2021, Ramsey et al. Nature Protocols, 2023, Lee et al. Psychopharmacology 2024). Using this model, we found that outbred CD1 mice, but not C57BL/6J mice, showed reliable social interaction self-administration, strong social-seeking behavior during isolation, and preference for social interaction over food. For this reason we used CD1 mice to identify brain regions that are active after operant social seeking (lever pressing for cues that were previously associated with the presence of a social partner). **Methods:** We trained outbred CD1 female mice to lever-press for palatable food pellets and then to lever-press under increasing fixed-ratio response requirements for access to a same-sex social partner. Next, we tested their motivation to seek cues associated with social interaction after 15 days of social isolation. We included two additional control groups that received identical training but stayed in their homecages on test day or were exposed to a separate novel context on test day. Homecage group was included to test for baseline levels of Fos expression, and novel context group was used to induce high levels of non-specific Fos expression. We extracted and perfused the mouse brains 90 minutes after initiation of behavioral testing and performed immunohistochemistry for Fos, an immediate early gene used as a marker of neuronal activity. We examine whole brain Fos expression to determine which areas are active in response to social seeking. **Results:** Social seeking induced high levels of Fos expression in several different cortical, striatal, and thalamic areas. We observed the highest fold change in the medial orbitofrontal cortex, prefrontal cortex, and nucleus accumbens core. Interestingly, Fos levels in the brain regions were similar or higher than Fos in response to novel context exposure. **Conclusion:** Our data suggest that social seeking induces high levels of neuronal activity in the brain, particularly in cortical and striatal regions. Future directions include using our recently bred CD1 hybrid FosTRAP2 mice to manipulate neuronal ensembles in highly active brain regions to determine which regions and/or circuits encode volitional social learning in mice.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: Conahcyt CF-2023-G-518

Title: Artificial vs. Natural Pacing: How D2 NAcSh Neuron Activation Alters Licking Microstructure

Authors: *N. REQUEJO-MENDOZA[1], J. LUIS-ISLAS[2], E. GIL-LIEVANA[3], J.-A. ARIAS-MONTANO[4], R. GUTIERREZ[5];
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Abstract: The nucleus accumbens shell (NAcSh) is pivotal in the neural circuitry of reward, influencing motivation, pleasure, and decision-making. Within the NAcSh, dopamine D2 receptor-expressing (D2 NAcSh) neurons are instrumental in modulating reward-driven behaviors. Despite this, the specific mechanisms by which D2 NAcSh neurons govern sucrose preference and licking behavior are not fully elucidated. This study utilized optogenetic activation and inhibition to explore the role of D2 NAcSh neurons in these behaviors across several paradigms. In a two-bottle freely licking assay, activation of D2 NAcSh neurons reduced the preference for a 3% sucrose solution, concurrently increasing water intake—indicative of a diminished sucrose reward valuation. Conversely, inhibition of these neurons did not affect sucrose preference. Further analysis in a 10% sucrose freely licking and laser frequency scanner test revealed that optogenetic activation, particularly at frequencies between 5-20 Hz, halted licking during the 1 s stimulation window, without altering overall consumption. Inhibition via ArchT, however, had no impact on licking behavior. Notably, self-activation of the laser at natural licking frequencies (7-8 Hz) did not disrupt the licking microstructure. This contrasted with the imposed stimulation at 8 and 20 Hz, which significantly disrupted licking, suggesting that the artificiality of experimenter-imposed rhythm compared to self-paced licking influences the behavioral outcome. In a brief access taste test employing various laser conditions (no laser, laser paired with each lick, 8 and 20 Hz experimenter-imposed), we observed that imposed stimulation at 20 and 8 Hz disrupted licking more than self-activated D2 NAcSh neuron stimulation at similar frequencies. This underscores that D2 NAcSh neuron activity predominantly affects licking when the stimulation is externally controlled rather than self-determined. Additionally, we established that D2 NAcSh neuron activation (but not inhibition) is inherently rewarding, as evidenced by an increase in the total number of trials in this task. A Real-time Place Preference test corroborated that D2 NAcSh neuron activation at 20 Hz (but not 8 Hz) is rewarding. Conversely, a negative reinforcement test indicated that neuron inhibition induces a negative valence signal. Our findings confirm the regulatory function of D2 NAcSh neurons in reward valuation, impacting both sucrose preference and licking microstructure, but only under conditions of artificial, experimenter-imposed optogenetic frequency, not during self-paced natural licking rhythms.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH T32DK128782
NIH R01DA025634

Title: Repeated conditioning progressively alters dopamine and behavioral responses to sucrose in taste aversion

Authors: *M. K. LOH[1], S. J. HURH[2], S. SCHRANK[2], J. P. SEVIGNY[2], D. R. SPARTA[2], M. F. ROITMAN[2];
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Abstract: Ingested stimuli resulting in illness are remembered and subsequently rejected (conditioned taste aversion; CTA). Dopamine release in the nucleus accumbens (NAc), driven by ventral tegmental area dopaminergic (VTA-DA) neuronal firing, is key for encoding food reward. How dopamine encoding changes for initially rewarding tastes linked to negative post-ingestive outcomes is unclear. Here, we expressed GRAB_DA2h in the NAc or cre-dependent GCaMP6s in the VTA of TH Cre+ rats to capture real-time dopamine release and VTA-DA activity, respectively via fiber photometry. Separately, we delivered cre-dependent tdTomato to the VTA of TH Cre+ subjects to fluorescently tag VTA-DA neurons. Brief (5s; 200µl) intraoral infusions of 0.3M sucrose (30 trials/session; 35-55s intertrial interval) were delivered. Rats were then injected (conditioning) with malaise-inducing LiCl (Paired) or saline (Unpaired). The next day, rats received the counterbalanced injection without sucrose infusions and were untreated the following day. This 3-day process was repeated twice. Photometry results revealed that sucrose-evoked dopamine release and VTA-DA activity were unchanged in Unpaired, but increasingly suppressed in Paired rats across conditioning days. Using a customized Deeplabcut model for pose-estimation tracking, Paired rats exhibited greater paw and nose responses (e.g. 'behavioral reactivity'), to intraoral sucrose across conditioning days. To assess VTA plasticity, in vitro recordings of spontaneous post-synaptic currents (PSCs) from VTA-DA neurons were made after conditioning. PSC amplitude and frequency were comparable between Paired and Unpaired rats. These results support differential dopamine responses for the same taste stimulus when it is rewarding versus aversive and suggest that the change in mesolimbic dopamine responses to sucrose in CTA is not mediated by shifts in presynaptic drive onto dopamine neurons within the VTA. Ongoing work aims to identify the source(s) of excitatory and inhibitory drive to VTA_{DA} that are altered by the development of CTA. Research supported by NIH T32DK128782 (MKL) and R01DA025634 (MFR).

Disclosures: M.K. Loh: None. **S.J. Hurh:** None. **S. Schrank:** None. **J.P. Sevigny:** None. **D.R. Sparta:** None. **M.F. Roitman:** None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.22/H11

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDDK DK085721

Title: Adolescent and Adult Age Differences in Palatable Food-Cue Learning and Consumption in Males and Females

Authors: *R. SHTEYN[1], G. D. PETROVICH[2];
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Abstract: Hunger and food palatability stimulate food intake and impact food-seeking and learning about food cues. We have found that hunger is not required for associative learning about a palatable food (PF; Test Diet pellets) in adults, and that females are more sensitive to PF than males, especially when sated. Adolescent and adult responding to food rewards can differ. Here we compared how adult and adolescent rats learn about and consume PF under sated and hungry conditions. Male and female adult (postnatal day (P) 81-83 at the start of the experiment) and adolescent (P32-34 at the start of experiment) Sprague Dawley rats were either food restricted (85% *ad libitum* body weight) or had *ad libitum* access to chow. Rats learned cue-food associations across 8 Pavlovian conditioning sessions, followed by cue-only presentations for 4 extinction sessions in a different context. They were then tested for renewal of conditioned responding to the food cue in the acquisition compared to extinction context. Before and after the learning-extinction-renewal protocol, rats were tested for consumption of PF and chow in their home cage (1h test/day/food; counterbalanced). There were age differences in consumption that were dependent on hunger state. Hungry adolescents and adults ate similar amounts of PF, but adults ate more PF than chow, while adolescents ate similar amounts of both foods. In contrast, sated adolescents ate more PF than sated adults, and ate more PF than chow. Females ate more PF than males. All groups successfully learned, extinguished, and renewed conditioned responding to the food cue. Across acquisition, adolescents responded more overall and during food cues. Sated adolescents responded more than sated adults, whereas hungry adults and adolescents responded similarly. Adolescent females had higher responding during early learning. During extinction, adolescents responded more than adults, during cue presentations and baseline, and adults reached baseline levels sooner than adolescents. During renewal tests, adolescents responded more than adults in both contexts. There were no sex differences during extinction training or renewal testing. Overall, adolescents responded more than adults throughout the learning and memory protocol, which is consistent with prior evidence that adolescents are more responsive to stimuli that predict reward than adults. Consumption test patterns suggest that sated adolescents are more sensitive to PF than sated adults. In contrast, hungry adolescents have a similar drive for both foods, whereas adults have a clear preference for PF. These findings also indicate that female sensitivity to PF is present during adolescence.

Disclosures: R. Shteyn: None. **G.D. Petrovich:** None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.23/H12

Topic: G.09. Drugs of Abuse and Addiction

Support: PHS grant DA06214

Title: Binge sucrose and saccharin-induced neuroadaptations: a focus on the orexin/hypocretin system

Authors: *D. DE SA NOGUEIRA[1,2], S. DELCOURTE[3], G. S. ASTON-JONES[3];
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Abstract: Binge eating disorder is the most common eating disorder and the neuronal mechanisms involved in this maladaptive behavior are not well known. Behavioral and molecular adaptations induced by eating disorders share commonalities with those involved in addiction. Given the links of the orexin/hypocretin system to reward processing/addiction and food intake, this study examined its contribution to binge-like eating in female rats. Four separate groups were used (i) intermittent access to food (12h), (ii) intermittent access to both food and 10% sucrose (12h), (iii) intermittent access to both food and 0.4% saccharin (12h), or (iv) continuous access to both food and sucrose; all access treatments were over for 28d. Only groups with intermittent access to either sucrose or saccharin displayed excessive intake in the first hour of testing (i.e., binge eating), as expected. Compared to the group with intermittent access to food only, all other groups exhibited increased numbers of orexin neurons. In parallel, 10, 20 or 30mg/kg of an orexin 1 receptor antagonist, SB334867, reduced binge-like intake in groups with intermittent access to sucrose or saccharin but not in rats with continuous access to sucrose. Inhibition of signaling in orexin projections to VTA using retrograde Gi DREADDs and 2mg/kg CNO i.p in in orexin-cre^{+} rats also decreased binge-like intake in both intermittent sucrose and saccharin groups. We then assessed whether binge-like intake altered economic demand for cocaine in females. Only intermittent access groups exhibited increased demand for cocaine. SB334867 (10 or 30 mg/kg, ip), or chemogenetic inhibition of orexin orexin projections to VTA, decreased demand for cocaine in groups with intermittent access to sucrose and saccharin. Altogether, our findings indicate that intermittent sucrose or saccharin access alters the orexin system in a manner similar to intermittent drugs of abuse. They also highlight the VTA as an orexin target that is involved in the increased binge behavior and demand after intermittent sucrose or saccharin. Hence, our results broaden the understanding of neural alterations associated with binge eating and support addictive-like properties of highly palatable food.

Disclosures: D. De Sa Nogueira: None. **S. Delcourte:** None. **G.S. Aston-Jones:** None.

Poster

PSTR127: Reinforcement, Learning, and Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR127.24/H13

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Rna sequencing analysis identifies differentially expressed genes in the medial prefrontal of rats after continuous and intermittent access to sucrose.

Authors: *J. ULYSSE[1], C. HILDENBRAND[2], V. GUJAR[3], A. DAIWILE[4], K. BEFORT[2], P. ROMIEU[2], J. L. CADET[5];
[1]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [2]Lab. de Neurosciences Cognitives et Adaptatives (LNCA), Univ. de Strasbourg, UMR7364, Ctr. Natl. de Recherche Scientifique (CNRS), Strasbourg, France; [3]Mol. Neuropsychiatry Res. Br., Natl. Inst. on Drug Abuse/NIH, Baltimore, MD; [4]MNRB, NIH, NIDA, Baltimore, MD; [5]Mol. Neuropsychiatry Res. Br., Natl. Inst. On Drug Abuse/ NIH, Baltimore, MD

Abstract: Binge-eating disorder (BED) affects millions of people around the world. Binge eating can cause morbid weight gain and metabolic anomalies. Higher sugar intake is often associated with depression, diabetes mellitus, cardiovascular disease, and cancer. In the present study, we have used the RNA sequencing approach to identify genes that might be associated with BED in a rat model of continuous or intermittent access to sucrose. Specifically, rats were assigned into three groups: one group was a control (CT) rats that had no access to sucrose; the second group was a continuous access group (CA) which had uninterrupted access to sucrose for 6 weeks; and the third group was an intermittent access group (IA) which fed for 6 weeks for 2-hour binge session for 3 times a week. The rats were euthanized three days after the last session and the medial prefrontal cortex was isolated for RNA-seq. The analysis of RNA-seq identified 663 up-regulated and 739 down-regulated genes in IA compared to CT. In addition, 773 up-regulated and 594 down-regulated genes were identified in the CA compared to the CT. Moreover, 735 up-regulated and 820 down-regulated genes were quantified in the IA compared to the CA. A more stringent cut-off of 1.5-fold changes identified 179 genes that were differentially expressed in the three pair-wise comparisons. These mRNAs include insulin receptor related receptor (INSRR), cubilin (CUBN), interferon induced transmembrane protein 1 (Ifitm1), cluster of differentiation-22 (CD22), and human R-spondin1 (RSPO1). Using IPA, we found that several of these genes were linked to eating disorders and severe obesity. These observations support the notion that intermittent access to sucrose could serve as an important model to discover targets for the treatment of BED.

Disclosures: J. Ulysse: None. **C. Hildenbrand:** None. **V. Gujar:** None. **A. Daiwile:** None. **K. Befort:** None. **P. Romieu:** None. **J.L. Cadet:** None.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.01/H14

Topic: G.03. Motivation

Support: This study was supported by the Intramural Research Program of the National Institute on Drug Abuse

Title: Role of Dorsal Raphe glutamatergic neurons in cocaine-seeking behavior

Authors: *M. BARBANO, J. QI, O. ESPINOZA, U. MOHAMMAD, M. CANDIDO, Jr., M. F. MORALES;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: The dorsal raphe nucleus (DR) is best known for containing serotonergic neurons, but it also contains other types of neurons, including glutamatergic neurons that express the vesicular glutamate transporter type 3 (VGluT3). We have previously demonstrated that DR-VGluT3 neurons establish excitatory monosynaptic connections with a subset of ventral tegmental area (VTA) dopaminergic neurons that project to the nucleus accumbens. We further demonstrated that VTA release of glutamate from DR-VGluT3 fibers induces release of dopamine in the nucleus accumbens and is rewarding. Here, by a combination of optogenetics, a conditioned place preference (CPP) task or a drug self-administration task, we investigated the extent to which DR-VGluT3 inputs to the VTA play a role in cocaine-seeking behavior. We injected viral vectors encoding channelrhodopsin-2 (ChR2), halorhodopsin (Halo), or the eYFP tag into the DR of different cohorts of VGluT3-Cre mice and implanted optic fibers aimed at the VTA. After CPP or self-administration training, we found that VTA release of glutamate from DR-VGluT3 fibers in ChR2 mice induced reinstatement of cocaine-seeking behavior. In contrast, VTA inhibition of glutamate release from DR-VGluT3 fibers in Halo mice prevented stress- and priming-induced reinstatement of cocaine-induced CPP. Given that we have previously demonstrated that VTA release of serotonin from DR neurons is rewarding, we next determined the extent to which DR serotonergic inputs to the VTA play a role in cocaine preference. For these studies, we injected viral vectors encoding either ChR2 or eYFP into the DR of different cohorts of SERT-Cre mice and trained them in the CPP task. We found that VTA release of serotonin from DR-SERT fibers in ChR2 mice had no effect on the reinstatement of cocaine-induced CPP. We conclude that VTA release of glutamate from DR glutamatergic fibers, but not VTA release of serotonin from DR serotonergic fibers, plays a critical role in the reinstatement of cocaine-seeking behavior.

Disclosures: M. Barbano: None. **J. Qi:** None. **O. Espinoza:** None. **U. mohammad:** None. **M. Candido:** None. **M.F. Morales:** None.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.02/H15

Topic: G.03. Motivation

Support: the Intramural Research Program of the National Institute on Drug Abuse

Title: Vta glutamatergic and gabaergic inputs from the pedunculopontine tegmental nucleus and their role in motivated behavior and on cocaine-induced conditioned place preference behavior

Authors: *H.-L. WANG[1], R. J. KULKARNI[1], Q. SHEN[1], B. LIU[1], M. F. MORALES[2]; [1]IRP/NIDA/NIH, Baltimore, MD; [2]Cell Neurobiol Res. Br., IRP, NIDA, NIH, Baltimore, MD

Abstract: Pedunculopontine tegmental nucleus (PPTg) is composed of cholinergic, GABAergic, and glutamatergic neurons, which provide inputs to ventral tegmental area (VTA). Here, we determined the extent to which PPTg glutamatergic or GABAergic neurons innervate the VTA. By VTA injection of retrograde track tracer fluorogold (FG) and phenotyping of $PPTg^{FG}$ neurons, we found that within the total population of $PPTg^{FG}$ neurons, ~52% expressed the vesicular glutamate transporter 2 (VGluT2), ~32% expressed glutamic acid decarboxylase (GADs) and ~5% expressed choline acetyltransferase (ChAT). We next assess the behavioral consequence of VTA photoactivation of $PPTg^{VGluT2}$ or $PPTg^{VGaT}$ fibers. We expressed channelrhodopsine (ChR2) in $PPTg^{VGluT2}$ neurons by PPTg injection of AAV2-DIO-ChR2-eYFP in VGluT2::cre mice or expressed ChR2 in $PPTg^{VGaT}$ neurons by PPTg injection of AAV2-DIO-ChR2-eYFP in VGaT::cre mice. We implanted optical probe in VTA to photoactivate $PPTg^{VGluT2}$ or $PPTg^{VGaT}$ fibers in behaving mice. ChR2-eYFP mice were tested in a three-chamber apparatus where they received optical stimulation when they entered the laser-paired chamber. We found that photoactivation of $PPTg^{VGluT2}$ to VTA pathway drove conditioned place aversion, photoactivation of $PPTg^{VGaT}$ to VTA pathway drove conditioned place preference. These data indicate that while VTA release of glutamate from $PPTg^{VGluT2}$ neurons plays a role in aversion, the VTA release of GABA from $PPTg^{VGaT}$ neurons plays a role in reward. Given that PPTg has been implicated in cocaine reward. Next, we determined the extent to which photoactivation of $PPTg^{VGluT2}$ to VTA or $PPTg^{VGaT}$ to VTA pathway modulates cocaine seeking behavior. We used conditioned place preference (CPP) procedure, and optically induced VTA release of glutamate or GABA from PPTg inputs during acquisition, expression or reinstatement phases of cocaine-induced CPP. We found that activation of $PPTg^{VGluT2}$ to VTA pathway did not affect acquisition of cocaine-induced CPP but inhibited expression and priming-induced reinstatement of cocaine behavior. VTA release of GABA from $PPTg^{VGaT}$ fibers did not change acquisition of cocaine-induced CPP but reinstated cocaine-induced CPP. We concluded that VTA glutamatergic and GABAergic inputs from PPTg play a role in cocaine-seeking behavior.

Disclosures: H. Wang: None. **R.J. Kulkarni:** None. **Q. Shen:** None. **B. Liu:** None. **M.F. Morales:** None.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.03/H16

Topic: G.03. Motivation

Support: IRP NIDA Program

Title: Lateral habenula co-release of glutamate and GABA from ventral tegmental are or entopeduncular nucleus: synaptic properties and their role in behavior

Authors: *S. HAHN[1], H.-L. WANG[2], R. GARCIA[3], S. ZHANG[4], B. LIU[5], M. F. MORALES[6]; [1]NIH/NIDA, Baltimore, MD; [2]IRP/NIDA/NIH, Baltimore, MD; [3]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [4]Natl. Inst. of Hlth., Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [5]Cell. Neurobiol Rese Br., IRP, NIDA, NIH, Baltimore, MD; [6]Cell Neurobiol Res. Br., IRP, NIDA, NIH, Baltimore, MD

Abstract: Lateral habenula co-release of glutamate and GABA from ventral tegmental area or entopeduncular nucleus neurons: synaptic properties and their role in behavior
Suyun Hahn, Huiling Wang, Raul Garcia, Shiliang Zhang, Bing Liu and Marisela Morales
Neuronal Networks Section, Integrative Neuroscience Research Branch, NIDA IRP
We have previously demonstrated that neurons co-expressing vesicular glutamate transporters 2 (VGluT2) and vesicular GABA transporter (VGaT) are present in the ventral tegmental area (VTA) and entopeduncular nucleus (EPN) and shown that single axon terminals from the dual neurons co-release glutamate and GABA in the lateral habenula (LHb). Here, we examined the LHb synaptic properties established by axons from dual glutamate-GABA neurons of the VTA and EPN. We expressed channelrhodopsin-2 in dual glutamate-GABA neurons of the VTA or EPN by using dual recombinase *vglut2-Cre/vgat-Flp* mice. By ex vivo electrophysiology, we found that LHb photostimulation of VTA VGluT2-VGaT terminals evoked local inhibitory postsynaptic currents (IPSCs) and excitatory postsynaptic currents (EPSCs). We detected three patterns of postsynaptic currents, in which the average amplitude was larger for IPSCs than for EPSCs. In contrast, LHb photostimulation of EPN dual terminals evoked larger EPSCs than IPSCs. Next, by applying different LHb photostimulation frequencies in VTA dual terminals, we found that the IPSC amplitudes were larger than EPSC amplitudes at all tested frequencies. In contrast, the amplitudes of EPSCs or IPSCs evoked by LHb photostimulation of EPN terminals were differentially affected by frequency stimulations, indicating different release probabilities of glutamate and GABA from distinct synaptic vesicles. We further determined that LHb photostimulation of VTA dual terminals hyperpolarized membrane potentials and inhibited firing activity in LHb neurons, but LHb photostimulation of EPN dual terminals evoked action potentials and membrane depolarization. By behavioral testing, we found that LHb photostimulation of the VTA or EPN dual terminals did not induce place preference or place aversion. Collectively, these results indicate that glutamate and GABA co-release from glutamate-GABA neurons of the VTA or EPN differentially inhibited or excited LHb, and do not seem to play a role in reward or aversion.

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Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.04/H17

Topic: G.03. Motivation

Support: NRF Grant 2022M3E5E8017804

Title: Inhibitory regulation of approach behavior in risky foraging requires temporally specific modulation of the central amygdala

Authors: *J. LEE, J.-S. CHOI;
Korea Univ., Seoul, Korea, Republic of

Abstract: In nature, the ability to forage while adeptly suppressing ongoing behavior when confronted by threats is necessary for survival. While the central nucleus of the amygdala (CeA) has been implicated in processing both aversive and appetitive stimuli, the specific mechanisms by which CeA activity suppresses ongoing behavior in response to an anticipated threat have been less studied. In a series of experiments, we tested the role of the CeA in suppressing foraging behaviors in rats by using a robot that mimics predatory attacks and creating threatening situations. Animals were trained to drink sucrose solution from the port guarded by the robot, with the robot attack delivered 6 s after the first lick. Fiber photometry revealed increased CeA activity during reward consumption, with further heightened activity observed in animals that withdrew their heads early enough to successfully avoid the robot's attack. We then investigated whether the heightened CeA activity was necessary for suppressing sucrose solution licking behavior by temporally inhibiting the CeA at discrete time points. Interestingly, inhibiting the CeA only during periods of heightened activity disrupted behavior suppression, leading to increased approaches to the port and sucrose consumption. Furthermore, inhibiting the CeA at these specific time points resulted in a higher number of approach failures, as animals were unable to avoid attack by withdrawing their heads early. Taken together, these findings suggest that the increased activity of the CeA at specific timing plays a critical role in suppressing approach behaviors and avoiding threats.

Disclosures: J. Lee: None. **J. Choi:** None.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.05/H18

Topic: G.03. Motivation

Support: NRF Grant 2022M3E5E8017804

Title: Activation of CGRP neurons in the parabrachial nucleus suppresses addictive behavior

Authors: *G. PYEON[1], J.-H. KIM[2], J.-S. CHOI[1], Y. JO[1];
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Abstract: Conventional methods of behavior modification to address addictive behaviors often involve methods like electric shocks, which may be effective but can cause potential harm due nociceptive pain. Neurons expressing calcitonin gene-related peptide in the parabrachial nucleus ($CGRP^{PBN}$) are known as general alarm signals that responds to aversive stimuli of diverse sensory modalities and provide affective pain signals. Here we investigated whether stimulating $CGRP^{PBN}$neurons could replicate the behavioral correction effects of electrical shocks, thereby curbing addictive behavior without eliciting nociceptive resposnes. Using *Calca*-Cre::DAT-Cre mice with channelrhodopsin-2 (ChR2) expressed in midbrain dopamine and $CGRP^{PBN}$ neurons, we first trained animals to press a lever for optical stimulation of dopamine cells (1s, 20Hz) until they developed addictive lever-pressing behavior (> 400 lever presses/hour). Then, each lever press triggered optical stimulation in the $CGRP^{PBN}$ neurons (3s, 30Hz) instead of stimulating dopamine cells. Upon activation of $CGRP^{PBN}$ neurons, the mice exhibited a significant reduction in lever-pressing behavior compared to control animals without ChR2 expression in $CGRP^{PBN}$ neurons. This also had a long-term effect, as the suppression effect of addictive-like behavior remained even 10 days after the last stimulation of $CGRP^{PBN}$. Next, we investigated whether activating $CGRP^{PBN}$ could also suppress addictive behavior in the context of actual drug use. We trained mice to self-administer cocaine intravenously (0.2 mg/kg) for over 10 days. Upon switching to $CGRP^{PBN}$ activation, we observed a similar reduction in lever-pressing, which sustained even after a 14-day abstinence period. Collectively, these results suggest that $CGRP^{PBN}$ neurons generate alarm signals in the brain that significantly curb addictive behavior and effectively suppress ongoing behavior.

Disclosures: G. Pyeon: None. **J. Kim:** None. **J. Choi:** None. **Y. Jo:** None.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.06/H19

Topic: G.03. Motivation

Support: Jim and Betty Ann Rodgers' Chair Fund
The Florida Department of Health James and Esther King Biomedical Research Program

Title: Effects of early-life nicotine exposure on motivated behaviors

Authors: *M. X. TRUPIANO[1], D. M. MCCARTHY[1], D. L. GRAHAM[1], L. PEETERS[2], R. W. BROWN[2], Y. WANG[1], G. D. STANWOOD[1], P. G. BHIDE[1];
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Abstract: Maternal smoking during pregnancy is a major public health concern due to potential adverse effects on both the mother and her offspring. Early-life nicotine exposure is associated with behavioral deficits such as inattention, hyperactivity, and impulsivity which are hallmark behavioral traits for attention deficit hyperactivity disorder (ADHD). Apart from cognitive deficits, individuals diagnosed with ADHD also exhibit apathy, which is a behavioral expression of motivational deficits in adolescents and adults. Motivational influences on cognition encompass both the external rewards' reinforcing effects on performance and the impact of intrinsic motivation derived from inherent satisfaction or interest in the activity. However, it remains unclear whether there is an association between prenatal exposure to nicotine and motivated behavior in children. To investigate this, we examined the consequences of early-life exposure to nicotine on motivated behaviors in a mouse model. Female Swiss Webster mice were exposed to plain drinking water or water containing nicotine (200 µg/ml) beginning 3 weeks before conception and continuing throughout pregnancy and nursing. We assessed approach-avoidance behavior, sensorimotor gating, spontaneous motivation, reinforcement, and anhedonia in adult male and female offspring. Early-life nicotine exposure produced significant deficits in multiple measures of motivated behaviors, demonstrating long-term consequences of life early-life nicotine exposure. Changes in neurotransmitter signaling mechanisms within the mesolimbic pathways may underlie the changes in motivated behaviors in this mouse model.

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Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.07/H20

Topic: G.03. Motivation

Support: NIH Grant DA057360

Title: Nucleus accumbens cholinergic interneurons and incubation of cue-induced cocaine seeking

Authors: *A. KAWA, S. J. WEBER, M. M. BEUTLER, M. E. WOLF;
Behavioral Neurosci., OHSU, Portland, OR

Abstract: Incubation of cocaine craving describes a progressive increase in cue-induced cocaine-seeking that occurs during abstinence following cocaine self-administration (SA). Previous work showed that incubation of craving is mediated in part by plasticity involving

medium spiny neurons in the nucleus accumbens (NAc). However, to date no studies have tested the role of NAc cholinergic interneurons (CIN) in incubation. This is being explored in transgenic rats expressing Cre recombinase under the control of the choline acetyltransferase (ChAT) promotor. We first determined that ChAT:Cre(+) rats do not differ from Cre- or wildtype rats in cocaine SA or incubation of cocaine craving. Studies are ongoing to test how chemogenetic excitation or inhibition of CIN in the NAc core affects cue-induced seeking before and after incubation has occurred. Preliminary results indicate that inhibiting CIN late in abstinence has no effect on seeking. Finally, we are using fiber photometry to record from CIN of the NAc core during cocaine seeking tests in early and late abstinence, as well as during food seeking tests following food SA.
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Disclosures: A. Kawa: None. **S.J. Weber:** None. **M.M. Beutler:** None. **M.E. Wolf:** Other; Founder of Eleutheria Pharmaceuticals LLC.

Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.08/H21

Topic: G.03. Motivation

Support: DA054449
DA055017
AA027555
AA014351

Title: Neuronal Ensembles Regulating Opioid-Motivated Approach and Avoidance Behavior

Authors: *H. NEDELESCU[1], C. MILIANO[2], M. W. BUCZYNSKI[3], S. AZUMA[4], G. E. WAGNER[5], F. WEISS[6], N. SUTO[7,8];
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Abstract: Opioid Use Disorder (OUD) is a chronic, relapsing brain disease characterized by compulsive drug seeking and use, engaging specific neurocircuits. One of the major projection systems implicated in regulating behavior motivated by drugs of abuse including opioids is the basolateral amygdala (BLA) pathway to nucleus accumbens (NAc). However, the BLA to NAc projection mediates not only approach behavior, as required for drug seeking, but also avoidance responses. This introduces the question as to the mechanisms by which a single excitatory projection system mediates diametrically opposite behaviors. Our preliminary data revealed that

morphine (a rewarding opioid agonist) and naloxone (an aversive opioid antagonist) recruit two distinct groups of neurons - neuronal ensembles or engrams - within the same (BLA) brain area. Moreover, selective activation of morphine vs. naloxone reactive BLA axon terminals in the NAc induced opposing conditioned place preference (CPP) and aversion (CPA) respectively. While these preliminary data establish a role for two discrete drug-reactive NAc-projecting BLA ensembles, a mechanism by which a single excitatory pathway orchestrates the execution of diametrically opposite behaviors remains to be elucidated. To address this, we employed *in situ* hybridization (RNA scope) to determine whether there are phenotypic genetic differences between the two projecting pathways. Finally, we employed an opto-dialysis method to determine whether neurotransmitters differed among the morphine- vs. naloxone-reactive ensembles, suggesting unique neurotransmitter combinations are released to support the diametrically opposing behaviors.

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Poster

PSTR128: Drugs of Abuse: Circuit Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR128.09/H22

Topic: G.03. Motivation

Support: Psi Chi Undergraduate Research Grant to S.P.

Title: Impulsive action is increased following the stimulation of nucleus accumbens μ-opioid receptors (but not CB1 receptors) in the rat

Authors: S. PATEL[1], E. HAWKINS[1], E. IRVIN[1], Y. TANG[1], ***W. E. PRATT**[2];
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Abstract: Situated between cortical and hypothalamic afferents and motor outputs, the nucleus accumbens (NAc) serves important roles in regulating appetitive and consummatory motivation, as well as action selection based on reinforcement history. Prior investigations have shown that lesion or inactivation of the NAc increases impulsive-like behavior in rodent models (e.g., Cardinal et. al, 2001; Feja, Hayn & Koch, 2014). Impulsivity is a defining feature of many behavioral disorders, including drug use. Many drugs of abuse are known to impact NAc function. However, the potential influence of specific receptor subtypes in the NAc on impulsive behavior has yet to be examined. In these experiments, we investigated the impact of stimulating the μ-opioid receptor or the cannabinoid-1 (CB1) receptor in the NAc on impulsive action in rats, as measured by a differential reinforcement of low rates of responding (DRL-20) schedule of reinforcement. Two groups of male Sprague-Dawley rats were food-restricted to 90% of their baseline body weight and trained through successive approximations to perform on a DRL-20 schedule for sugar reinforcement. In this schedule, rats were reinforced for the first lever press,

and then obtained subsequent sugar reinforcement only if they withheld responding on the active lever for a full 20 seconds before pressing the lever again. Any press of the active lever reset the 20-second clock. Once trained, rats received surgical implantation of guide cannulas targeting the NAc core (coordinates relative to bregma: with the skull flat, +1.3 mm anterior, +/- 1.6 mm lateral, with the injection site at -7.5 mm ventral from the skull). Following a one-week recovery period, rats were food-restricted once more, retrained on the task, and subsequently tested after drug injections. Separate groups received injections of the μ-opioid receptor agonist DAMGO (at 0.0, 0.025, or 0.25μg/side) or WIN55212-2 (at 0.0, 0.1, 0.5, or 1.0 μg/side) across multiple treatment days. Neither stimulation of μ-opioid receptor nor CB1 receptors significantly affected the total number of active lever presses during the 1-hr sessions. However, μ-opioid receptor stimulation significantly reduced the number of reinforcers earned within the drug session [$F(2,22) = 8.45$, $p = .002$], leading to impaired efficiency in achieving the sugar pellet [$F(2,22) = 7.03$, $p = .004$]. In contrast, CB1 receptor stimulation with WIN55212-2 did not impact the reinforcers earned or the efficiency measure [n.s.]. These data corroborate a role for the nucleus accumbens in impulsive action and suggest that opioid, but not cannabinoid, receptor activation in this region enhances impulsive-like behavior.

Disclosures: S. Patel: None. **E. Hawkins:** None. **E. Irvin:** None. **Y. Tang:** None. **W.E. Pratt:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.01/H23

Topic: G.04. Emotion

Support: Hong Kong Research Grant Council General Research Fund [17600522]

Title: Evaluating the Effects of tDCS on Depressive and Anxiety Symptoms from a Transdiagnostic Perspective: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Depressive and anxiety symptoms are prevalent among patients with various clinical conditions, resulting in diminished emotional well-being and impaired daily functioning. The neural mechanisms underlying these symptoms, particularly across different disorders, remain unclear, limiting the effectiveness of conventional treatments. Therefore, it is crucial to elucidate the neural underpinnings of depressive and anxiety symptoms and investigate novel, effective treatments across clinical conditions. Transcranial direct current stimulation (tDCS) is a

neuromodulatory technique that can help understand the neural underpinnings of symptoms and facilitate the development of interventions, addressing the two research gaps at both neural and clinical levels. Thus, this systematic review and meta-analysis aims to evaluate the existing evidence regarding the therapeutic efficacy of tDCS in reducing depressive and anxiety symptoms among individuals with diverse clinical diagnoses. This review evaluated evidence from fifty-six randomized, sham-controlled trials that administered repeated tDCS sessions with a parallel design, applying a three-level meta-analytic model. tDCS targeting the left dorsolateral prefrontal cortex (DLPFC) at 2-mA intensity demonstrates moderate efficacy in alleviating depressive symptoms, identifying the left DLPFC as a transdiagnostic neural mechanism of depressive symptoms across clinical conditions. In comparison, the findings on anxiety symptoms demonstrate greater heterogeneity. In conclusion, tDCS over the left DLPFC is effective in reducing depressive symptoms and shows promising effects in alleviating anxiety symptoms among individuals with diverse diagnoses. These findings enhance our understanding of the neuropsychological basis of depressive and anxiety symptoms, laying the groundwork for the development of more effective tDCS interventions applicable across clinical conditions.

Disclosures: E. Zheng: None. **N. Wong:** None. **T. Lee:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.02/H24

Topic: G.05. Mood Disorders

Title: Triple network connectivity changes in patients with major depressive disorder versus healthy controls via structural network Imaging after electroconvulsive therapy treatment

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Abstract: Objective: To investigate the effect of electroconvulsive treatment (ECT) on dynamic structural network connectivity in major depressive disorder (MDD), based on the triple-network model.**Methods:** Twenty-one first-episode, drug-naïve patients with MDD and 21 age- and sex-matched healthy subjects were recruited. Bilateral electrical stimulation was performed thrice a week for a total of 4-5 weeks in the MDD group. MRI data were obtained, and triple-network structural connectivity was evaluated using source-based morphometry (SBM) analysis. A paired t-test was used to analyze structural connectivity differences between pre- and post-ECT MDD groups, one-way analysis was used to calculate three intrinsic network differences between HCs, pre- and post-ECT groups, and partial least squares structural equation modelling was used to investigate dynamic structural network connectivity (dSNC) across groups.**Results:** Pre-ECT patients with MDD exhibited significantly lower salience network (SN) structural connectivity ($p = 0.010$) than the healthy control (HC) group and after ECT therapy SN structural connectivity was significantly elevated ($p = 0.002$) in post-ECT group compared with pre-ECT. PLS-SEM

analysis conducted on inter-network connectivity in the triple-network model indicated a significant difference between SN and central executive network (CEN) in all three groups. The HC and post-ECT MDD groups showed notable direct connectivity between the SN and default mode network (DMN), while the pre-ECT MDD group showed consequential pathological connectivity between the CEN and DMN. A mediation analysis revealed a significant indirect effect of the SN on the DMN through the CEN ($\beta = 0.363$, $p = 0.008$) only in the pre-ECT MDD group.**Conclusions:** ECT may be an effective and minimally invasive treatment for addressing structural changes in the SN and direct communication abnormalities between the three core brain networks in patients with MDD, with possible beneficial correction of indirect connections.

Disclosures: E. Chibaatar: None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.03/H25

Topic: G.05. Mood Disorders

Support: NIH R01-MH127006
NIH K01-MH116364

Title: Non-emotional salience responses elucidate systemic arousal state disruptions in the depressed brain.

Authors: *M. MOCCHI[1], E. BARTOLI[1], J. F. MAGNOTTI[2], J. DE GEE[3], B. A. METZGER[1], B. PASCUZZI[4], S. PULAPAKA[1], R. MATHURA[1], W. K. GOODMAN[5], S. A. SHETH[1], M. J. MCGINLEY[6], K. BIJANKI[1];
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Abstract: Patients with Major Depressive Disorder (MDD) exhibit disrupted cortical responses to emotionally salient stimuli in salience network (SN) nodes such as the anterior cingulate (ACC) and anterior insular (aIC) cortices. Sensory and autonomic responses to non-emotional stimuli are also disrupted, which may suggest that MDD symptomatology is rooted in a global dysfunction of arousal state. However, it is currently unclear how salience response disruptions in the SN are related to sensory and autonomic salience components, or why mood-related disruptions may be tracked by autonomic responses. Here, we aim to characterize the relationship between disrupted responses in SN and sensory regions and identify which response components are tracked by autonomic activity. To do this, we recorded local field potentials (LFPs) in SN and auditory sensory regions including posterior supratemporal gyrus (pSTG), aIC, and ACC, while simultaneously capturing pupil diameter during a non-emotional auditory

oddball task. Response amplitudes were extracted for both standard and oddball trials. Patients were then grouped by depression status, and both cortical and pupil response amplitudes were examined between and within subjects. The pSTG sensory region exhibited intra-stimulus high gamma and post-stimulus alpha-beta response components, which were both tracked by pupil diameter responses at the trial level. While high gamma responses showed no difference between depression cohorts, the alpha-beta response was reduced in depressed patients. Differences in alpha-beta responses across depression status are reflected in pupillary response size. Convergent evidence is seen in the SN, whereby different response components correspond to the high gamma and beta-alpha components in the pSTG and are differentially tracked by pupil diameter responses. These data provide compelling evidence that MDD symptomatology may be driven by global disruptions in arousal, which may elucidate the mechanism by which we can non-invasively track depression severity using autonomic measures.

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Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.04/H26

Topic: G.05. Mood Disorders

Title: Small-world network models of resting-state prefrontal cortex functional connectivity in depression

Authors: *K. TIWARI[1], M. S. PHATAK, Sr.[2], S. JAISWAL[3], A. PATIL[4];
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Abstract: Problem Statement: This study aims to explore prefrontal cortical connectivity dynamics in depression, crucial due to its significant influence on depression and associated cognitive impairment. Despite cognitive symptoms' importance, current antidepressants have limited efficacy. Thus, this research aims to uncover nuanced connectivity patterns to inform targeted interventions, potentially improving treatment outcomes and quality of life for individuals with depression.
Method: We recorded 10 minutes of resting-state prefrontal cortical activity with eyes closed in individuals with major depressive disorder (Group D, n=10, age 26.4±6.47 years) and in healthy, age-matched controls (Group N, n=10, age 26.0±7.02 years) using functional near-infrared spectroscopy. Depression scores were assessed using the Hamilton Depression rating Scale, and Montreal Cognitive Assessment was used to assess cognitive impairment. Using a customized matlab script we developed multiple small-world network-based functional connectivity models

using average hemoglobin levels and frequency bands(10 bands from 0.01 to 0.40 hz) for all optodes.
Result:Statistical analysis showed no significant age or cognitive score differences between groups. However, Group D exhibited significantly higher depression scores (p-value = 0.00003), indicating moderate depression (mean score: 14.4 ± 4.03). Analysis of average hemoglobin data revealed significantly reduced connectivity across prefrontal cortex regions in individuals with depression. Frequency-based analysis indicated generally lower functional connectivity in depression across all bands, especially in lower frequencies, contrasting with healthier individuals displaying more diverse connections. Despite having fewer connections overall, depressed individuals showed stronger connectivity in the connected areas.
Conclusion:We found that individuals with depression, despite scoring within normal ranges on traditional cognitive tests, exhibit reduced functional connectivity at rest within the prefrontal cortical areas. Furthermore, functional connectivity varies across frequency domains among individuals with depression. At lower frequencies, areas are less connected compared to normal, though connectivity is stronger at higher frequency bands, albeit with fewer connected areas. These findings highlight deranged functional connectivity that warrants monitoring during depression treatment.

Disclosures: K. Tiwari: None. **M.S. Phatak:** None. **S. Jaiswal:** None. **A. Patil:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Program #/Poster #: PSTR129.05/H27

Topic: G.05. Mood Disorders

Support: NIH MH108705

Title: Passive heating causes larger increases salivary cortisol Levels in patients with depression

Authors: *K. SUDHEIMER;
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Abstract: Cortisol dysregulation in major depression is commonly observed. One lesser-known mechanism that affects the amount of cortisol that can be observed in saliva is the binding of cortisol to corticosteroid-binding globulin. A large reservoir of cortisol is stored in the blood in a protein-bound state in which it cannot bind to target tissues. Corticosteroid-binding globulin is responsive to changes in blood temperature, releasing portions of the cortisol reservoir as blood temperature rises. This unbound cortisol can then be detected in saliva. Excessive heat exposure can overwhelm the body’s ability to maintain a stable core body temperature. It is unclear if exposure to excessive heat causes higher salivary cortisol levels in patients with depression compared to healthy participants.
Unmedicated patients with major depression (N=8) and health participants (N=18) underwent

60-degree C heat exposure for up to 45 minutes. This causes significant increases in core body temperature (tympanic membrane), heart rate, and cortisol in saliva. Patients with depression had a significantly greater increase in salivary cortisol compared to healthy controls during the heat exposure. Curiously, 30 minutes after the heat exposure, when core body temperature had returned to baseline, salivary cortisol levels continued to rise in healthy participants but normalized in patients with depression.
These results suggest that the temporal dynamics of heat-related corticosteroid-binding globulin cortisol release and/or heat-related HPA axis activity may contribute to the patterns of cortisol dysregulation commonly observed in major depression.

Disclosures: K. Sudheimer: None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Topic: G.05. Mood Disorders

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Title: A network analysis of the symptom-level connection between postpartum depression and mother-to-infant bonding

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Abstract: Postpartum depression and mother-to-infant bonding difficulties (MIBD) are two pivotal issues impacting maternal and infant mental health. They often coexist and are bidirectionally interlinked, complicating the understanding of their interaction. This study uses network analysis to explore the intricate connections between these two conditions at the individual symptom level. We analyzed data from 5,594 postpartum Japanese women, whose geographical distribution was nationally representative. Graphical LASSO was used to construct regularized partial correlation networks for the entire dataset and stratified subgroups by postpartum period. Our analysis identified 'sadness' as a persistent central symptom, with 'fear' and 'enjoyment' as key bridge symptoms linking postpartum depression and MIBD. Notably, unique symptom patterns emerged in specific postpartum periods: in the first 6 months, 'anger' and 'crying' were central symptoms while 'overwhelm' was a bridge symptom; from 7 to 12

months, 'anger' and 'indifference' were central symptoms while 'self-harm' was a bridge symptom; from 13 to 24 months, 'crying' and 'insomnia' were central symptoms while 'laugh' was a bridge symptom. Our analysis reveals both consistent and period-specific symptoms, highlighting the shifting dynamics across different postpartum stages. These insights offer valuable implications for targeted interventions that consider the temporal context in addressing postpartum depression and MIBD.

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Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.07/H29

Topic: G.05. Mood Disorders

Title: Proteomics to dissect the molecular mechanisms underlying major depressive and bipolar disorder

Authors: *F. ROIG KUHN[1], F. KOOPMANS[2], R. KLAASSEN[3], D. WEVER[4], I. R. HOLTMAN[5], A. B. SMIT[6], S. SPIJKER[7];
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Abstract: The neuropsychiatric disorders major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ) are leading causes of disability globally. These disorders have partially overlapping symptoms, complicating diagnosis, and often lead to inaccurate treatment. Identifying what sets them apart at the molecular level can improve diagnosis and therapies to manage their impact on quality of life. Here, we performed a quantitative proteomics analysis on the Netherlands Brain Bank Psy-cohort (n=170 patients with MDD, BD, SZ (n=13-30 per disease), and controls), comprising grey matter of the superior temporal (GTS) and frontal gyrus (GFS), from donors with extensive clinical data compiled in the Netherlands Neurogenetics Database. The brain areas chosen were previously implicated in these disorders. Our aims were to 1) establish a molecular profile of disease status to find global disease-specific markers, and 2) use these profiles to cluster patients and examine how much these disease types overlap based on their molecular signature. Patient-clustering based on >6000 high confidence identified and quantified proteins (peptide detection rate 75%; >2 peptides per protein) from these two brain areas showed a clear separation based on tissue type, and age. Clustering based on the top-50 proteins regulated in each disease showed mild separation based on disease status. Analysis per tissue type with age as co-factor showed the most differentially regulated proteins between

patients and controls for GFS tissue (2% of proteome; FDR q-value 0.01). GOAT analysis revealed overrepresentation of upregulated proteins involved in synaptic transmission and downregulated metabolic processes. Surprisingly, MDD showed clear post-synaptic protein dysregulation compared to BD (SYNGO analysis). These high-content proteomics techniques can offer new insights into dysregulated proteins and pathways in the brain and potentially lead to discovering new targets for more effective treatment.

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Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Program #/Poster #: PSTR129.08/H30

Topic: G.05. Mood Disorders

Title: Eye movements during structured and unstructured tasks discriminate youth with depressive disorder from healthy controls

Authors: *B. K. NOYES[1], L. BOOIJ[2], H. C. RIEK[1], I. C. PITIGOI[1], J. HUANG[1], D. BRIEN[1], B. C. COE[1], B. J. WHITE[1], S. KHALID-KHAN[1], D. P. MUNOZ[1];
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Abstract: Up to 29% of youth worldwide report symptoms of subthreshold depression (subD), which can be defined as two to four symptoms of depression lasting for two weeks or more, accompanied by a decrease in quality of life or overall health. In clinical practice, subD is an underserved, underrecognized, and undertreated condition that urgently requires additional research. Understanding the neurological underpinnings of this condition is critical for development of early treatment interventions before symptoms escalate to major depressive disorder (MDD). The aim of our study is to search for behavioural markers of youth with subD and MDD, which will be accomplished through video-based eye-tracking; to identify impairments in cognitive control, arousal, and attention. Thus far, 85 healthy controls (64 female; M=16.8yrs; Patient Health Questionnaire [PHQ]=1.95) and 28 outpatients with MDD (22 female; M=16yrs; PHQ=14.79) have been enrolled. Participants completed two tasks: 1) the Interleaved Pro-Anti Saccade Task (IPAST) to investigate impairments in cognitive control; and 2) the unstructured Free-Viewing (FV) video task to investigate differences in attention and arousal. Each IPAST trial included a central fixation spot whose colour (green or red) indicated whether participants were to make a pro-saccade (look toward peripheral stimulus) or anti-saccade (look away from the stimulus), respectively. In the FV task, participants watched 10 min of neutral video clips (e.g., cityscapes, nature) and 10 min of clinical-oriented video clips (e.g., emotional faces, food/eating, alcohol/drinking). Finally, participants completed self-report questionnaires for psychiatric symptoms. Preliminary data suggests that during IPAST, youth

with MDD had slower saccadic reaction time and more errors than control participants during anti-saccade trials, showed abnormal pupil responses, and blinked more during fixation. During FV, data suggest that youth with MDD have longer fixation durations, less center bias, and generate fewer saccades. Future analyses will seek to determine the effect of sex, gender, and age on these outcomes. Eye tracking may be an easy, inexpensive, and useful tool for probing network functioning in youth with MDD and provides a rationale for using eye-tracking to study the neurological impairments among youth with subD.

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Poster

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Program #/Poster #: PSTR129.09/H31

Topic: G.05. Mood Disorders

Support: IRP-NIMH-NIH
ZIAMH002857
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NCT00397111

Title: Cortisol and emotional face processing in differing levels of suicide risk

Authors: *S. LAMONTAGNE[1,2], J. R. GILBERT[1,2], L. NEELY[1,2], L. WALDMAN[1,2], C. A. ZARATE, Jr.[1,2], E. BALLARD[1,2];
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Abstract: Interpersonal issues are a major risk factor for a suicide crisis, including an impaired ability to process emotional cues. Dysregulated cortisol output, which is observed among those with suicidal thoughts and behaviors (STBs), can influence how individuals perceive and respond to social cues. This suggests that cortisol might impact neural underpinnings of emotional face processing patterns, but this has yet to be examined in relation to differing levels of suicide risk. One hundred eighteen participants were assigned to one of the following four suicide risk categories: Crisis: those with a suicide attempt and/or ideation with intent in the past two weeks (n=14), Past Attempt: those with a history of attempt, but no suicidal behavior or ideation with intent in the past year (n=39), Clinical Control: those with anxiety or mood symptoms, but no suicide history (n=35), and Healthy Control: those without psychiatric or suicide history (n=30). 24-hour urinary cortisol was analyzed using tandem liquid chromatography and mass spectrometry. A CTF 275-channel whole-head magnetoencephalography (MEG) scanner was used to examine electrophysiological correlates of

emotional face processing. During MEG scanning, participants completed an emotional evaluation task in which they responded to facial stimuli. MEG data were source-localized in the gamma (30-58 Hz) frequency (a proxy measure of excitation-inhibition balance). Results showed that cortisol levels were blunted in the Past Attempt (ps<0.05) but not the Crisis group compared to controls. Adjusting for cortisol levels, task-based reaction times (RTs) in the explicit conditions were faster for positive than negative face stimuli in all groups except for the Crisis group, where RTs were similar across stimuli. This suggests that cortisol interacts with acute suicide risk to disrupt emotion recognition and processing, perhaps reflecting a diminished ability to differentiate between positively and negatively valanced facial expressions. Electrophysiologically, main effects of Group in the early visual cortex (EV) and superior frontal gyrus (SFr) (ps<0.01, cluster corrected) revealed diverging activation patterns by suicide risk. Across conditions, the at-risk groups showed higher gamma power than the control groups in the EV but lower gamma power in the SFr. These findings suggest that those with active and past STBs have heightened initial processing but disengaged higher-order processing of emotional cues. Disrupted connectivity parameters between these regions might be linked to cortisol dysregulation, which could underlie future efforts to identify biomarkers of risk.

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Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Program #/Poster #: PSTR129.10/H32

Topic: G.05. Mood Disorders

Title: Comparing data-driven subtypes of depression informed by symptom and neuroimaging data

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Abstract: The wide clinical and neurobiological heterogeneity of depression points to the presence of subtypes within the disorder. However, subtyping efforts have not reached a consensus. Our study aims to compare several previously developed data-driven depression subtyping approaches within the same subject space to evaluate similarities in subtype solutions.We applied the subtyping approaches of two studies that clustered on symptom data. Briefly, Maglanoc et al 2019 performed Gaussian mixture discriminant analysis on and Lamers et al 2010 performed latent class analysis. We also applied the subtyping approaches of two studies that clustered on functional neuroimaging data. Price et al 2017 performed a group iterative multiple model estimation on networks and Drysdale et al 2017 performed hierarchical

clustering on nodes related to depression measures. We applied these approaches in the same UK Biobank sample (N=2299) with moderate or severe depression. We evaluated the agreement of the resulting cluster solutions between approaches using adjusted rand index and determined what phenotypes each subtyping approach is sensitive to using ANOVAs, including demographic data, clinical measures, and neuroimaging features.The optimal subtype solutions for each approach are in Fig. 1A. The agreement between clustering approaches is in Fig. 1B. There was almost no overlap of cluster solutions between any approach which indicates how impactful analytical decisions are in subtyping efforts. Fig. 1C shows how little the phenotypes that differed significantly in each approach overlap. However, all the approaches were sensitive to many phenotypes, indicating the clusters are capturing meaningful heterogeneity. All in all, this work indicates different subtyping approaches capture different sources of heterogeneity that do not have a direct relationship to other sources of heterogeneity.

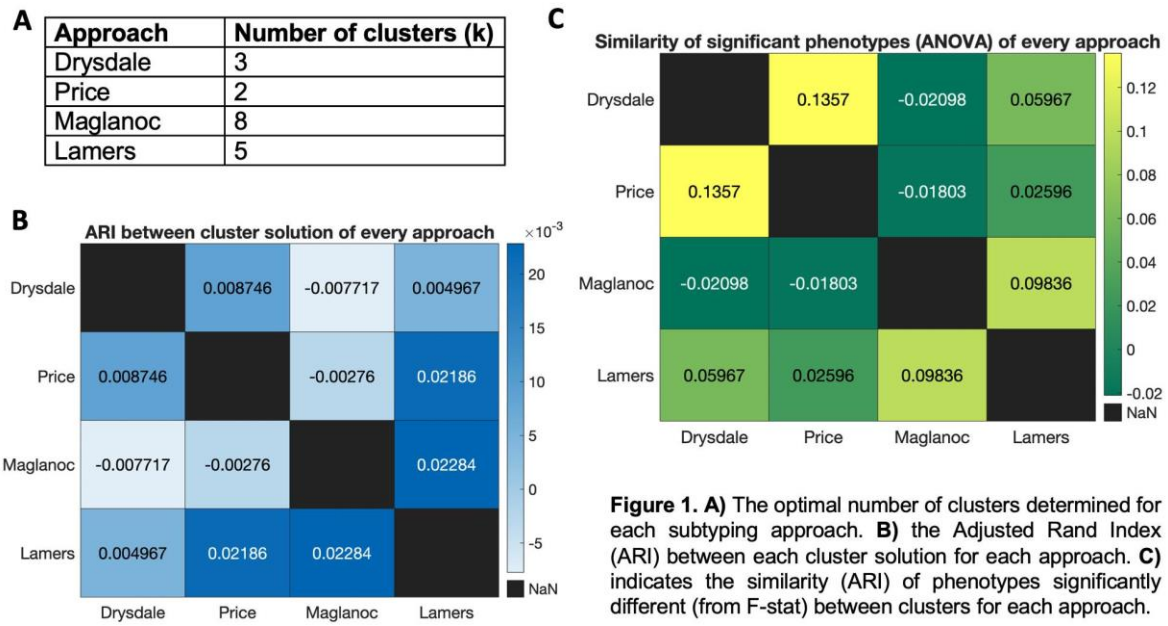

Figure 1. A) The optimal number of clusters determined for each subtyping approach. **B)** the Adjusted Rand Index (ARI) between each cluster solution for each approach. **C)** indicates the similarity (ARI) of phenotypes significantly different (from F-stat) between clusters for each approach.

Disclosures: K. Hannon: None. **L. Balogh:** None. **F. Ahmad:** None. **P. Lenzini:** None. **A. Sotiras:** None. **J. Bijsterbosch:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.11/H33

Topic: G.05. Mood Disorders

Support: NIH Grant

Title: The role of head motion in t1-weighted structural mri analysis: effects on depression phenotypes in the uk biobank

Authors: *C. SHELTON[1], P. LENZINI[1], S. PARK[2], A. SOTIRAS[1], J. BIJSTERBOSCH[3]; [1]Radiology, Washington Univ. in St. Louis, Saint Louis, MO; [2]Radiology, [3]Washington Univ. in St. Louis, St. Louis, MO

Abstract: Head motion is widely recognized as a significant source of artifacts in functional MRI (Power et al., 2012), leading to substantial efforts for correction (Parkes, 2018; Prium, 2015). However, the effects of head motion on structural MRI (sMRI) analyses are less emphasized. Nevertheless, prior work has shown that motion impacts sMRI quality (Alfaro-Almagro et al., 2021) and has been associated with clinical and cognitive phenotypes (Gilmore, 2021). We aimed to determine whether controlling for head motion affected brain-behavior associations in sMRI analyses. We analyzed data from 25,828 UK Biobank participants to assess how head motion during MRI scans affects structural brain imaging results. We quantified head motion using 21 variables from structural MRI, resting-state fMRI, diffusion MRI, and task-based fMRI, including measures such as mean absolute, median absolute, and 90th percentile values—both absolute and relative—averaged across space and time. Linear regression was performed to link image-derived phenotypes from T1 structural MRI (assessing volumes, areas, and thicknesses in Desikan-Killiany Atlas regions; Miller et al., 2016) to clinical phenotypes, including depression (RDS-4; Dutt, Hannon et al., 2022), controlling for age, sex, site, and total intracranial volume. Linear regressions were repeated before and after including head motion parameters as confounding variables, and regression coefficients and FDR-corrected p-values were compared before and after correcting for head motion. Our findings indicated that mean resting-state fMRI had the largest impact of all head motion variables. Controlling for mean resting-state fMRI head motion notably altered brain sMRI associations with depression. Before controlling for head motion, 76 out of 186 sMRI imaging-derived phenotypes were significantly associated with depression after FDR correction. However, 14 out of 76 associations between depression and imaging-derived phenotypes no longer reached FDR-corrected significance after controlling for head motion, including associations with rostral anterior cingulate volume and entorhinal cortex thickness. The normalized regression coefficients of all 76 imaging-derived phenotypes in association with depression were smaller (i.e., closer to zero) after correcting for head motion, with an average drop in normalized coefficient of 0.016. These results suggest that without motion correction, the impact of these regions on depression-related symptoms may be overestimated.

Disclosures: C. Shelton: None. **P. Lenzini:** None. **S. Park:** None. **A. Sotiras:** None. **J. Bijsterbosch:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.12/H34

Topic: G.05. Mood Disorders

Title: Decoding Adolescent Depression with Machine Learning Insights from Neuroimaging Data

Authors: *A. CAMASSA[1], O. CARRIOLI[2], M. WAGNER[2], T. J. SEJNOWSKI[1,3];
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Abstract: Given the escalating prevalence of depression among pre-adolescents and adolescents, there is a pressing need for reliable and accessible diagnostic approaches. This urgency is compounded by the growing availability of brain imaging data, which paves the way for pioneering diagnostic protocols grounded in Machine Learning (ML) methodologies. In this context, we propose an ML-driven methodology for discerning depression in pre-adolescents utilizing functional magnetic resonance imaging data (fMRI). Our approach is inspired by the Multi-voxel pattern analysis (MVPA) that allows to detect differences between conditions with higher sensitivity than conventional univariate analysis commonly used in neuroimaging studies. Drawing from the Adolescent Brain Cognitive Development study (ABCD), we specifically utilize beta weights derived from task fMRI data within subcortical and cortical regions as delineated by the Desikan atlas. The chosen task, the EN-back task, encompasses memory and emotion regulation processes across nine distinct conditions. Our cohort comprises 215 healthy subjects and an equal number of adolescents afflicted with depression, aged 9-10 years. We have devised a computational pipeline facilitating the evaluation of various binary classifiers and feature selection techniques across all available conditions. Our repertoire includes Support Vector Machine (with linear, radial basis function, and polynomial kernel), Random Forest, Multi-Layer Perceptron, AdaptiveBoosting, Naive Bayes, and K-Nearest Neighbors, coupled with recursive feature elimination and features permutation. Our findings reveal commendable classification accuracy across all conditions, with the most proficient models being Support Vector Machine and Multi-Layer Perceptron, trained using permutation feature selection method. This pipeline holds promise for extension to the classification of other mental disorders. These results mark the emergence of innovative diagnostic tools grounded in ML, ready to enhance computational psychiatry through the identification of physiological biomarkers for mental disorders, thereby improving their diagnosis and treatment.

Disclosures: A. Camassa: None. **O. Carrioli:** None. **M. Wagner:** None. **T.J. Sejnowski:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.13/H35

Topic: G.05. Mood Disorders

Support: R21MH126197

Title: Reference points, a computational instantiation of reward expectations, predict the severity of major depressive disorder (MDD)

Authors: *L. WU, A. VITTALA, D. LIEBERS, E. TELL, D. YAN, X. SONG, K. LOUIE, C. M. RAIO, D. IOSIFESCU, P. W. GLIMCHER;
NYU Grossman Sch. of Med., New York, NY

Abstract: Maladaptive responses to rewards and losses have been suggested as phenotypes across psychiatric disorders. A central element of decision theories is the reference point (RP), an implicit benchmark against which objective outcomes are valuated. While computational psychiatry has laid the groundwork for linking mathematical models of human decision-making to behavioral pathologies, the RP – and its potential role as a transdiagnostic marker - has received very little attention. Neurophysiological correlates of the RP have been identified in the monkey avACC (Hayden et al., 2011), and response to antidepressants has been associated with a specific patterns of activity in this same area (Hamani et al., 2011). Because individuals with an elevated RP may experience even highly valued prospects as negative reinforcers, we hypothesized that a pathologically high RP is a marker of MDD.
We examined behavioral RPs in 50 MDD patients and 70 healthy controls (HCs). To assess the static RP, we used a gamified foraging task based on the marginal value theorem in which subjects forage for apples in an orchard for 5-minute blocks (Constantino and Daw, 2015). This task both defines an optimal strategy for any orchard and reveals the precise number of apples a given participant experiences as non-reinforcing. To assess the dynamics of the RP, we used a value adaptation task (Khaw et al., 2017) to examine how efficiently subjects recalibrated their RP to dynamic changes in the local value context.
In the foraging task, MDD patients (vs. HC) showed a systematic shift of the RP (long-delay condition: 5.9 vs. 3.7 apples, $p < 0.001$; short-delay condition: 6.5 vs. 4.7, $p < 0.001$). Using only 5m of data, we found that individual RPs were strongly correlated with depression severity as measured by the gold standard Montgomery-Asberg scale of depression ($r = 0.71$, $p < 0.001$). In the value adaptation task, the RP showed pathological levels of stability in MDD patients. Specifically, the increased RP following high value adaptation in HCs began decaying to adapt to a new reward environment within a minute, while MDD patients showed no measurable sensitivity to the environment over 15m (MDD vs. HC; time constant: 0.03 vs. -0.88, $p < 0.001$). Fits to a divisive normalization model verified these differences, with a reduced effect of recent stimuli in MDD (vs. HC; influence parameter: -0.006 vs. 0.014, $p = 0.03$).
Together, these results suggest that pathologies of the RP may be both a valid marker of severity and a critical component of the phenomenology of MDD. These easy to deliver computational psychiatric tools may also provide simple assays relevant to the diagnosis and treatment of MDD.

Disclosures: L. Wu: None. **A. Vittala:** None. **D. Liebers:** None. **E. Tell:** None. **D. Yan:** None. **X. Song:** None. **K. Louie:** None. **C.M. Raio:** None. **D. Iosifescu:** None. **P.W. Glimcher:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.14/H36

Topic: G.05. Mood Disorders

Support: Ramathibodi Grant RF66138
AIMC Grant 32080009

Title: Exploring Hippocampal- Prefrontal GABA relationship: A Pilot MRS Study in the Thai Transgender Depression Cohort

Authors: *K. TAM[1], S. JARUKASEMKIT[2];
[2]Intrnl. Medicine, Ramathibodi Hosp., [1]Mahidol Univ., Bangkok, Thailand

Abstract: Previous studies have shown decreased GABA concentration in anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) in major depressive disorder (MDD) (Abdallah, C. G. et al, 2015). While the GABA-level of the hippocampus is underexplored, there is evidence of hippocampal- prefrontal circuit role in emotional dysregulation as well as volume loss in chronic stress exposure. As a pilot study from a Thai Transgender cohort, 20 trans-women were included for investigation of GABA Magnetic Resonance Spectroscopy (MRS) and depression feature and severity. Inclusion criteria are trans- women, aged ≥ 18 years with Patient Health Questionnaire-9 (PHQ-9) > 9. All participants undergo MRS for GABA and answer 19 psychological questionnaires. MEGA-PRESS GABA-edited sequence by 3 Tesla Philips - Elition Ingenia were acquired by voxel of interest volume 3x3x3 cm^3 placed in left hippocampus (extended to amygdala) and left DLPFC with TR 1600 ms, and TE 68 ms. Preprocessing was performed by Philips software. The average age is 30.1 (STD ± 6.5) years, average PHQ-9 score is 14.9 (IQR 8.5). Results revealed significant level-log regression with motion control between hippocampus GABA/Cr level and Rumination Response Scale - Reflection (RRS-R) at $\beta = -0.53$ ($p = 0.02$), PHQ- 9 at $\beta = -0.52$ ($p = 0.03$), and Montgomery Asberg Depression Rating Scale (MADRS) at $\beta = -0.5$ ($p = 0.03$). DLPFC GABA/Cr concentration was negatively correlated with Anxiety Sensitivity Index -3 (ASI-3) at $\beta = -0.5$ ($p = 0.04$). Due to limitation of statistical power, there was no significant relationship between hippocampus and DLPFC GABA/Cr. Psychopathology model proposed by Hasler and Northoff, has discussed the decrease in GABA levels associated with increased rumination and stress sensitivity, consistent with our results in the hippocampus and DLPFC (Hasler & Northoff, 2011). However, while the model proposed that generally decreased GABA levels are associated with depressive symptoms, this study suggests region-specific GABA might lead to different depressive features. Limitation lies in small sample size and technicality in hippocampus GABA signal processing. Further studies will increase sample size and explore the mediator effect between GABA MRS and other modalities of imaging in depression psychopathology.

Disclosures: K. Tam: None. **S. Jarukasemkit:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.15/H37

Topic: G.05. Mood Disorders

Support: NIMH R01128306

Title: Altered resting-state functional connectivity of the locus coeruleus in individuals with depression and anhedonia symptoms.

Authors: *G. IRIZARRY, J. N. ADAMS, B. LEONARD, D. ZHOU, S. J. GRANGER, L. TRONDSEN, M. A. YASSA;
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Abstract: Anhedonia is a transdiagnostic symptom associated with depression, reflecting the loss of pleasure. Dysfunction of the locus coeruleus (LC), a brainstem nucleus that is the main source of norepinephrine in the brain, may be one neural substrate of anhedonia. The LC modulates arousal and valence, known to influence the hippocampus (HC) and amygdala (AMY) in memory processes. Prior resting-state functional connectivity (rs-FC) studies in anhedonia have found altered FC between areas associated with reward modulation. We aimed to assess whether the rs-FC of the LC with HC and AMY is (1) altered in individuals with depression in comparison to controls, and (2) associated with higher anhedonia symptoms. Resting state fMRI data was analyzed from 63 participants (16 individuals without depression, 47 individuals with depression; mean age: 22.9 years; range 18-37 years; 76% female). fMRI data were preprocessed and analyzed using the CONN toolbox. For the LC we used a previously established metamask ROI, and HC and AMY ROIs were from the Brainnetome Atlas. Seed-to-seed FC was calculated for LC-HC (rostral and caudal HC ROIs), and LC-AMY (medial and lateral AMY ROIs). Seed-to-voxel analyses of the LC ROI were thresholded at p-uncorrected <0.005 and cluster size (k) of >25 voxels. We then used an exploratory latent factor approach based on the Beck Depression Inventory II and Beck Anxiety Inventory to characterize symptoms into classes, focusing on depression and anhedonia factors. In separate analyses, FC was compared between controls and individuals with depression, and anhedonia scores were correlated with FC. Sex was included as a covariate. Compared to controls, individuals with depression had lower FC between LC and left caudal HC ($t=2.55$, $p=0.007$). Across all participants, lower FC between LC and left caudal HC were significantly correlated with BDI anhedonia scores ($r=-0.22$, $p=0.04$) and the depression factor ($r=-0.22$, $p=0.047$). We did not find any significant associations between LC-AMY. Seed-to-voxel analysis showed increased BDI anhedonia scores were associated with lower FC between LC and a cluster including the left hippocampus and parahippocampal gyrus ($k=30$, peak p-unc<0.0001), and higher FC between LC and a cluster including the right caudate nucleus and cingulate cortex ($k=112$, peak p-unc<0.0001). These results suggest individuals with greater anhedonia severity may have different LC-HC modulation of memory retrieval. Understanding neurobiological mechanisms of LC rs-FC in depression could help develop targeted treatments for anhedonia.

Disclosures: G. Irizarry: None. **J.N. Adams:** None. **B. Leonard:** None. **D. Zhou:** None. **S.J. Granger:** None. **L. Trondsen:** None. **M.A. Yassa:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.16/Web Only

Topic: G.05. Mood Disorders

Title: Nonlinear connectivity measures characterize functional brain network features in major depressive disorder

Authors: *S. KHAZEI[1], Y. SHADMANESH[1], A. GHADERI[2];
[1]isfahan Univ., ISFAHAN, Iran, Islamic Republic of; [2]York Univ., Toronto, ON, Canada

Abstract: Major depressive disorder (MDD) remains a formidable public health challenge. It appears thatfunctional brain networks are involved in MDD. Current research suggests that disruptions withinfunctional brain networks may play a critical role in MDD pathophysiology. In this study, we examinedhow brain networks may change in MDD compared to normal individuals (without mental disorderswho were diagnosed through clinical interview along with diagnostic tests based on DSM5). Since itisn't certain which features may change between these two groups, we use the linear and nonlinearmeasures of functional connectivity to find out which of them can separate these two groups moreefficiently.In this study, EEG were recorded from 52 individuals (16 participants with MDD and 36 in the normalcontrol group). Then sLORETA algorithm was used to find current densities of EEG in 84 corticalBrodmann areas. Then, we used three measures (lagged nonlinear connectivity, lagged coherenceand lag phase synchronization) to construct networks for each individual. We then calculated twonetwork indices (clustering coefficient and global efficiency) and compared these measures betweentwo group using t-tests across different frequency bands (delta, theta, alpha, beta1, beta2, beta3 andgamma).The most significant differences in clustering coefficient and global efficiency between two groupswere observed when the lagged nonlinear connectivity was used for network construction. Thesesignificant differences were observed in the delta, theta, alpha, beta1, beta2, and gamma frequencybands. Using lagged coherence, significant differences were only observed in the beta3 band whilethe lagged phase synchronization revealed significant differences in the alpha, beta3, and gammabands. These findings suggest that the nature of connectivity alteration in MDD is mostly nonlinearand cannot be determined with linear connectivity measures such as lagged coherence.Furthermore, this nonlinear connectivity alteration may suggest the involvement of a complexcortical information propagation which is related to MDD.

Disclosures: S. Khazei: None. **Y. shadmanesh:** None. **A. Ghaderi:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.17/H38

Topic: G.05. Mood Disorders

Support: DARPA N660012324006

Title: Individuals with and without suicidal ideation exhibit differences in N400 during suicide-related sentence processing

Authors: *C. MCDANIEL[1], B. CAHN[2], W. JEONG[3], T. MCGEE[8], T. MEDANI[4], R. LEAHY[5], K. LERMAN[6], D. BYRD[7], I. BLANK[9], S. NARAYANAN[4], A. HABIBI[1];
[1]Psychology, [2]Psychiatry & the Behavioral Sci., [3]Biomed. Engin., [4]Electrical and Computer Engin., [5]Electrical and Computer Engineering, Biomed. Engineering, and Radiology, USC, Los Angeles, CA; [6]Computer Science, Information Sci. Inst., USC, Marina del Rey, CA; [7]Linguistics, USC, Los Angeles, CA; [8]Psychology, [9]Psychology, Linguistics, UCLA, Los Angeles, CA

Abstract: The present study investigated the neural markers of suicidal ideation using an EEG event-related potential (ERP) paradigm. 84 participants (age 18-25) completed questionnaires assessing symptoms of depression (PHQ-9) and suicidal ideation (Suicide Ideation Scale). Based on their scores, participants were categorized into a healthy control group (n = 35), depressed (non-suicidal) group (n = 23), or suicidal group (n = 26). In the EEG task, participants read 160 self-referential (first-person) sentences from one of four topics: neutral biographical information, depressive reflections, actions relating to depression, or suicidal ideation and intent. Sentences consisted of 80 minimal pairs differing only in the last word, which determined the sentence content (e.g., inclination or disinclination for suicide). Sentences were presented word-by-word and ERPs were time-locked to the presentation of the final word. Participants indicated whether they agreed (indicating *congruity*) or disagreed (indicating *incongruity*) with each sentence. For biographical sentences, we observed an expected increase in N400 amplitude in response to incongruent compared to congruent sentences in all three groups ($p < .001$). For sentences about suicidal ideation and intent, the control group responded much differently than the suicidal group, endorsing approximately 5% of sentences indicating suicidal inclination and approximately 90% of sentences indicating suicidal disinclination, as opposed to the suicidal group who endorsed approximately 50% of both types of sentences. In addition, only for this class of sentences, we observed a significant group by congruity interaction on N400 amplitude ($p < .001$): while all groups demonstrated similar N400 amplitudes for incongruent sentences, the control group showed increased N400 amplitudes compared to the suicidal group for congruent sentences ($p = .005$, Bonferroni-corrected). This increased N400 response was related primarily to the endorsement of sentences indicating a disinclination for suicidality. We did not observe these ERP differences for incongruent sentences, or for the other sentence topics, indicating that the findings are specific to congruent sentences priming suicide-related content. These results suggest that individuals without suicidal ideation may exhibit greater semantic processing demands when seeing congruent sentences priming suicide-related content, but that suicidal participants show no such processing changes. This research may indicate an ERP-based marker of suicidal ideation, which may aid in the effective identification of at-risk groups.

Disclosures: C. McDaniel: None. **B. Cahn:** None. **W. Jeong:** None. **T. Medani:** None. **R. Leahy:** None. **K. Lerman:** None. **D. Byrd:** None. **I. Blank:** None. **S. Narayanan:** None. **A. Habibi:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

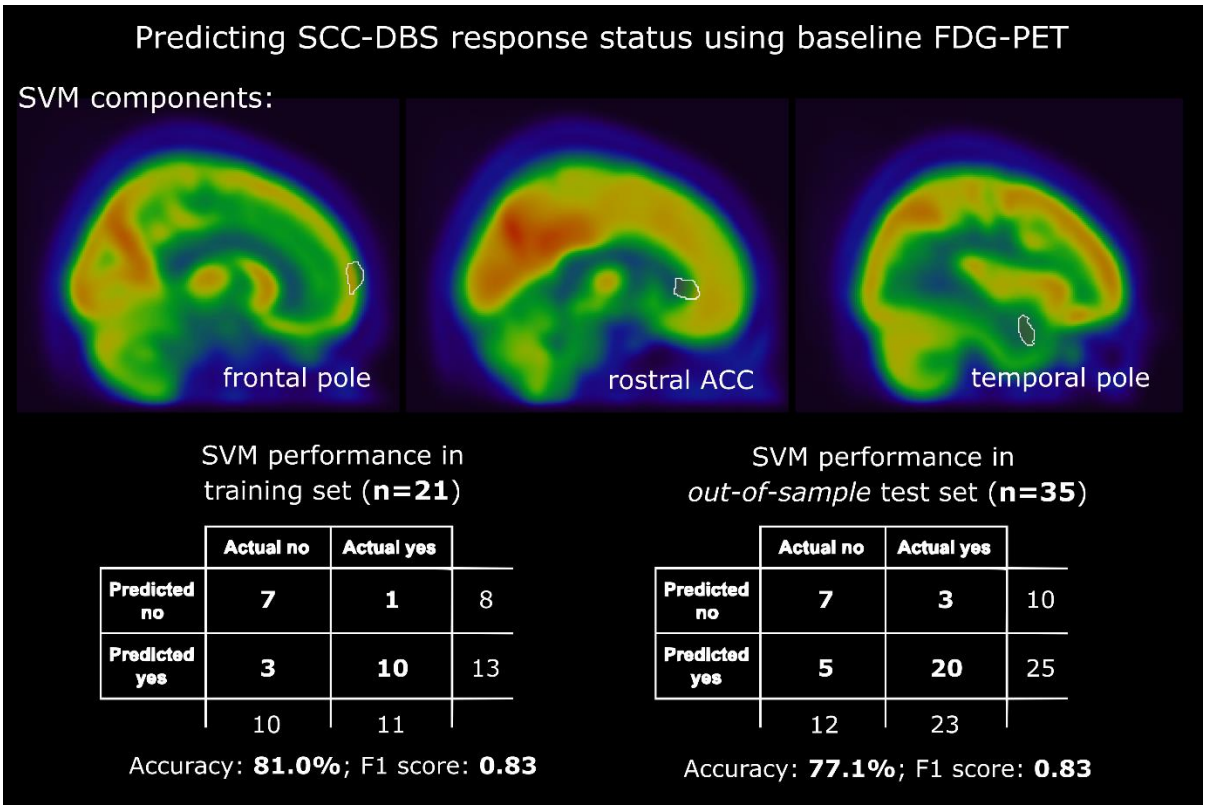
Program #/Poster #: PSTR129.18/H39

Topic: G.05. Mood Disorders

Title: Validating cerebral glucose metabolism as a pre-operative predictor of response to subcallosal cingulate deep brain stimulation

Authors: *G. J. B. ELIAS[1], A. M. LOZANO[2], J. GERMANN[3];
[1]Dept. of Med. Imaging & Div. of Neurosurg., Univ. of Toronto, Toronto, ON, Canada; [2]Dept Neurosurg., Toronto Western Hosp. Rm 4-431 West, Toronto, ON, Canada; [3]Div. of Neurosurg., Dept. of Surgery, Univ. Hlth. Network, Toronto, ON, Canada

Abstract: Major depressive disorder is a prevalent and highly debilitating condition associated with high rates of resistance to conventional treatments. Deep brain stimulation (DBS) - a neurosurgical intervention that is widely used to modulate dysregulated brain networks in movement disorders - has emerged as a potential therapeutic option for treatment-resistant depression (TRD). DBS targeting the subcallosal cingulate area (SCC-DBS) has received considerable attention in the last two decades, with numerous open-label trials yielding promising results. However, the failure of the largest randomized controlled trial to date and the fact that only between half and two thirds of treated patients achieve meaningful response (≥50% improvement from baseline) has highlighted the need for biomarkers that can help to optimize SCC-DBS. Our group previously investigated the utility of pre-operative 18F-fluorodeoxyglucose(FDG)-PET images for predicting post-SCC-DBS outcomes in 21 TRD patients (mean age: 48.3±9.1, 67% female) (https://doi.org/10.1093/brain/awab284), finding that glucose metabolism values from key brain areas could be coupled with supervised machine learning to retrospectively classify treatment response after 12 months of continuous stimulation. The current study applied our previously derived FDG-PET support vector machine (SVM) model to a larger, out-of-sample TRD cohort (n=35; mean age: 44.9±9.5, 60% female). This tripartite model, incorporating glucose metabolism values from rostral anterior cingulate cortex, frontal pole, and temporal pole, classified response status with 81.0% accuracy (76.9% precision; 90.9% recall; 0.83 F1 score) in the training cohort (n=21) and 77.1% accuracy (80.0% precision; 87.0% recall; 0.83 F1 score) in the out-of-sample test cohort (n=35). These results reinforce and extend our earlier findings, suggesting that FDG-PET-based predictive models of SCC-DBS treatment response may be generalized to unseen patient cohorts and could potentially inform patient selection and other treatment decisions in future trials.



Disclosures: G.J.B. Elias: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gavin Elias holds intellectual property in the field of deep brain stimulation. **A.M. Lozano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Andres Lozano holds intellectual property in the field of deep brain stimulation and is the co-founder of Functional Neuromodulation.. F. Consulting Fees (e.g., advisory boards); Andres Lozano is a consultant for Boston Scientific, Medtronic, and Abbott.. **J. Germann:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.19/H40

Topic: G.05. Mood Disorders

Support: NINDS Grant 1K23NS124978-01A
The Children's Health CCRAC Early Career Award
The Brain and Behavior Research Foundation Young Investigator Award
CTSA Pilot Award

Title: The striatal compartments, striosome and matrix, have distinct influences on resting state functional networks

Authors: *A. SADIQ[1], A. FUNK[2], J. L. WAUGH[3];
[1]Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Pediatrics, Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [3]Pediatrics, Univ. of TX Southwestern, Dallas, TX

Abstract: The striatum is divided into two interdigitated tissue compartments, the striosome and matrix. These compartments exhibit distinct anatomical, neurochemical, and pharmacological characteristics and have separable roles in motor and mood functions. Identifying compartment-specific functions is essential to understanding striatal diseases that selectively injure striosome or matrix. We set out to map the functional networks of striosome-like and matrix-like voxels in humans in vivo. We utilized scans from the Human Connectome Project, including all subjects that had full complements of diffusion MRI and resting state fMRI data. We eliminated subjects with a history of illicit substance use or alcohol use meeting criteria for Alcohol Use Disorder, yielding a cohort of 675 healthy adults. We utilized probabilistic diffusion tractography to identify voxels with striosome-like and matrix like patterns of structural connectivity. We then investigated the brains' resting state functional connectivity (rsFC) using striosome-like and matrix-like voxels as seeds. We found significant differences in rsFC between striosome- and matrix-like voxels ($p < 0.05$, FWE corrected for multiple comparisons), suggesting that striosome and matrix occupy distinct functional networks. Striosome-seeded networks exhibited ipsilateral dominance, while matrix-seeded networks included both hemispheres but were dominant in the contralateral hemispheres. We found that rsFC between the striatum and nucleus accumbens was dominated by the striosome in both hemispheres. Additionally, we identified compartment-specific engagement with the triple network (salience, executive control, and default mode networks (DMN). The anterior insula (a primary node of the salience network) had significantly higher rsFC with striosome-like than matrix-like voxels. The inferior and middle frontal cortices (primary nodes in the executive control network) showed divergent results by hemisphere: stronger rsFC with matrix-like voxels on the left, and striosome-like voxels on the right. Functional connectivity with DMN nodes was dominated by striosome-like voxels. Striosome injury likely manifests different motor, cognitive, and behavioral symptoms than matrix injury. Moreover, compartment-specific rsFC abnormalities may be identifiable before disease manifests at the whole-striatum level. Localizing these rsFC differences provides an anatomic substrate for understanding how the tissue-level organization of the striatum underpins complex brain networks, and how compartment-specific injury may contribute to the symptoms of specific neuropsychiatric disorders.

Disclosures: A. Sadiq: None. **A. Funk:** None. **J.L. Waugh:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.20/I1

Topic: G.05. Mood Disorders

Title: Isolating the 'P' Factor: A lesion analysis

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Abstract: Evidence suggests that psychiatric disorders such as depression and anxiety exist on a continuum. A general factor of psychopathology (p-factor) has been proposed as a latent variable representing the covariance among multiple psychiatric domains including internalizing, externalizing, and thought dysfunction. However, few studies have examined whether there are underlying neural correlates of the p-factor. Thus, this study aims to determine the neural correlates of the p-factor using the Iowa Scales of Personality Change (ISPC) in patients with focal brain lesions. Participants included 204 subjects from the Iowa Neurological Patient Registry (50.5% women, mean age 63.8 years). The ISPC is a collateral measure of personality changes following a brain lesion. There are five domains of personality traits including executive function, social function, distress, irascibility, and hypo-emotionality comprised of thirty items on the ISPC. Each brain lesion was manually traced and transformed to a common template brain (MNI152). We used multivariate lesion-symptom mapping with sparse canonical correlation analysis (LESYMAP) to investigate the neuroanatomical correlates of the P factor. Then, we generated structural and functional lesion network maps. The results from both the structural and functional lesion network maps converged and suggest that damage to the frontal pole is associated with a greater p-factor, indicating higher levels of general psychopathology. Understanding the causal neural mechanisms underlying the p-factor could help identify patients at risk for increased psychopathology after brain damage or neural structures that could serve as targets for neuromodulation.

Disclosures: A. Thomas: None. **M. Bowren:** None. **D. Tranel:** None. **K. Langbehn:** None. **A.D. Boes:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR129.21/I2

Topic: G.05. Mood Disorders

Support: NIMH 5R01MH121384-02

Title: Altered Dynamic Network Stability in Remitted Late-life Depression

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Abstract: Background: Late-life depression (LLD) is associated with negative outcomes including cognitive decline. However, the neurobiological changes underlying cognitive decline in LLD are not well understood. Disequilibrium in large-scale brain networks such as the default mode network, cognitive control network, and anterior salience network may contribute to cognitive changes observed in LLD. However, the dynamic interactions between these networks have not previously been examined in LLD. **Methods:** In this study healthy elders and participants in early remission from a documented major depressive episode were recruited as part of the REMBRANDT clinical trial. At the time of entry all participants completed a resting state and task-based fMRI and neuropsychological testing. Participants were followed to monitor for depression recurrence. Using a previously described machine learning algorithm, recurring whole-brain states of spatial co-activation were identified by k-means clustering. From identified co-occurring network states the duration within network state was calculated for healthy controls (n= 40) and LLD participants who remained in remission (n= 50) or experienced recurrence of depressive symptoms (n = 33). **Results:** A three-network solution with anatomical overlap with the salience network, default mode network, and cognitive control network best explained network activity. Compared with never depressed elders, participants who had experienced at least one episode of LLD exhibited decreased stability and altered transitions between networks without changes in the overall time spent in each network. Network stability correlated with neuropsychological markers of cognition. **Conclusions:** Collectively, these data suggest that an episode of late life depression produces alterations in dynamic network stability lasting into remission. Furthermore, stability of specific networks states is associated with neuropsychological outcomes which may predict the likelihood of a recurrent episode of LLD.
Funding Sources: NIMH 5R01MH121384-02

Disclosures: D. Homiack: None. **B.D. Boyd:** None. **A. Zhang:** None. **C. Andreescu:** None. **O.A. Ajilore:** None.

Poster

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Topic: G.05. Mood Disorders

Support: NRF MSIT. 2022M3E5E8018285
ABCD data 10.15154/1523041

Title: Differential Functional Connectivity Patterns of Insula Subregions in Pediatric Generalized Anxiety Disorder and Depression

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Abstract: Introduction The region known as the insula, associated with interoceptive awareness, plays a crucial role in emotional experiences beyond mere physical sensation recognition. Particularly in depressive and anxiety disorders, the disruption of interoceptive processes distorts emotional experiences. This complex relationship between the function of the insula and emotions underscores the necessity for thorough neuroscientific exploration. While previous studies have predominantly focused on the insula as a whole, our research aims to investigate specific subregions: the ventral anterior insula (vAI), dorsal anterior insula (dAI), and posterior insula (PI), exploring the differential patterns in depressive and anxiety disorders. We hypothesize that the specialized areas of the insula, due to their distinct functional roles, may exhibit varying patterns of functional connectivity when comparing patients with major depressive disorder (MDD) and generalized anxiety disorder (GAD).
Method Utilizing data from the Healthy Brain Network(version 10.0) and the Adolescent Brain and Cognitive Development (ABCD) Studies(version 4.0), we analyzed resting-state fMRI of 55 with Major Depressive Disorder (MDD) and 76 children diagnosed with Generalized Anxiety Disorder (GAD) aged 9-12. Connectivity patterns within insula subregions were examined using seed-based analyses with SPM12 and the CONN toolbox. The regions of interest (ROIs) specified were the left vAI (-33, 13, -7), the right vAI (32, 10, -6), the left dAI (-38, 6, 2), the right dAI (35, 7, 3), the left PI (-38, -6, 5), and the right PI (35, -11, 6).
Results Children with MDD showed increased connectivity between the left dAI and regions key for self-awareness and emotional processing, such as the precuneus cortex, cingulate gyrus, and cerebellum. This suggests a potential link between these neural connections and typical depressive symptoms, including negative self-perception and difficulties with emotional regulation. On the other hand, children with GAD exhibited stronger connections between the right PI and the right Rolandic operculum, areas associated with sensory processing. This enhanced connectivity may contribute to altered sensory perceptions and heightened responses to anxiety in GAD, reflecting the intense stress and anxiety these children experience.
Conclusion Our findings reveal distinct connectivity patterns in the insula's subregions, associated with self-regulation and sensory processing in pediatric depression and anxiety. This emphasizes the insula’s role in the complex neurobiology underlying these disorders, offering insights into targeted interventions.

Disclosures: J. Park: None. **E. Kim:** None. **M. Oh:** None. **Y. Lee:** None. **W. Lee:** None. **H. Park:** None.

Poster

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Program #/Poster #: PSTR129.23/I4

Topic: G.05. Mood Disorders

Support: DARPA Grant N660012324006

Title: Utilizing D-BIAT for Discrimination of Control, Depressed, and Suicidal Individuals: Preliminary Findings

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Abstract: Objective: This study aims to evaluate the effectiveness of the Death-Brief Implicit Association Task (D-BIAT) in distinguishing between control, depressed, and suicidal states among undergraduate students. Given the significant mental health challenges posed by depression and suicidal ideation, particularly among young adults in educational environments, early identification of at-risk individuals is essential for targeted interventions and support.
Methods: Ninety-five undergraduate students were recruited and categorized into control (n=36), depressed (n=29), and suicidal (n=30) groups based on scores from the Patient Health Questionnaire-9 (PHQ-9) and the Suicidal Ideation Scale (SIS). Participants completed the D-BIAT, a computerized task designed to measure implicit associations with death-related stimuli. Reaction time and D-scores were analyzed across D-BIAT blocks (Life:Me and Death:Me) for all three groups. Additionally, Receiver Operating Characteristic Area Under the Curve (ROC-AUC) values were computed from D-scores to assess discriminative power.
Results: Preliminary analysis indicated that participants at risk of suicide exhibited faster reaction times (i.e., shorter reaction times) on the "death:me" blocks compared to the "life:me" blocks, suggesting stronger implicit associations with death-related stimuli. Furthermore, D-score analysis revealed a heightened association between the self and death among the suicidal risk group, followed by depressed group in comparison to control. ROC-AUC analysis demonstrated promising discriminative ability, with AUC values of 0.62 for control vs. depressed, 0.63 for control vs. suicidal, and 0.625 for control vs. clinical (depressed and suicidal), while discriminability between depressed and suicidal was lower (AUC = 0.52).
Conclusion: The D-BIAT exhibits potential as a sensitive measure for detecting implicit associations with death-related stimuli among undergraduate students experiencing depressive and suicidal states. Further validation studies are necessary to refine the D-BIAT and maximize its utility as a screening tool for identifying at-risk individuals within educational settings.

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Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Program #/Poster #: PSTR129.24/I5

Topic: G.05. Mood Disorders

Support: University of Arkansas Vice Chancellor for Research and Innovation
Arkansas Biosciences Institute

Title: Characterizing the medial forebrain bundle structure in adolescents with depression

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Abstract: Major Depressive Disorder (MDD) is a prevalent and disruptive malady. While previous research on MDD has highlighted functional deficits in dopaminergic signaling from the Ventral Tegmental Area (VTA) to the Nucleus Accumbens (NAcc), less research has focused on their structural connection. Moreover, research has not identified whether structural changes to the VTA-NAcc tract might precede or follow MDD. Here we analyzed raw data from the Adolescent Brain Cognitive Development (ABCD) study to characterize the VTA-NAcc tract in early adolescents. We processed raw diffusion Magnetic Resonance Imaging (MRI) data from the baseline timepoint when participants were 9-years old. Brain volumes-of-interest were identified with FreeSurfer subcortical segmentation of the NAcc and the Pauli atlas of the VTA. We registered the VTA region from template-to-native space by aligning them with each participant's T1 anatomical scan using Advanced Normalization Tools (ANTs). We then seeded these brain volumes in constrained spherical deconvolution-based probabilistic tractography with MRtrix. The tractography results allowed us to visualize the VTA-NAcc tract in each hemisphere of every participant, and further to extract Fractional Anisotropy (FA) of the tract along its trajectory. The depression subscale of the Child Behavior CheckList (CBCL) indicated participants with depression (t score $\geq$ 60), leading to a final sample of 2,357 control participants and 207 with depression. We found lower coherence of the VTA-NAcc tract in the right hemisphere in adolescents with depression at trending statistical significance ($t(245) = 1.75$, $p = 0.08$). These results invite additional exploration of the countervailing cortical projections to the NAcc and their potential links to subtypes of depression.

Disclosures: T. Nguyen: None. **E.H. Ellis:** None. **J.K. Leong:** None.

Poster

PSTR129: Depression: Neural and Physiological Mechanisms

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Program #/Poster #: PSTR129.25/I6

Topic: G.05. Mood Disorders

Support: University of Illinois Chicago Honors College
University of Illinois, College of Medicine, Department of Psychiatry
the CoNECt Lab

Title: Exploring meteorological influences on neuropsychological outcomes in mood disorders

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Abstract: This interdisciplinary study bridges psychology and climatology to investigate the impact of weather on mood disorders in the Chicagoland area. Utilizing a sample of 87 participants, including 66 with mood disorders and 21 healthy controls, the correlation between meteorological conditions and daily self-reported energy and mood levels was examined. Participants rated their mood and energy on a scale of 1 to 10, while weather parameters such as temperature, precipitation, and snowfall were sourced from the National Oceanic and Atmospheric Administration for the period of April 2021 to May 2023. Quantitative analysis revealed a significant inverse relationship between energy levels and adverse weather conditions, specifically low temperatures and high precipitation ($p = 0.023$). A similar trend, though not statistically significant, was observed with mood levels ($p = 0.061$), suggesting weather's potential role in daily mood swings in individuals with mood disorders. The findings underscore the importance of considering environmental factors in mental health care and highlight the need for targeted interventions that integrate meteorological data into predictive models of mood disorders. This study contributes to the understanding of weather's impact on mood disorders and emphasizes the significance of interdisciplinary research in addressing complex public health challenges.

Disclosures: Z. Jabri: None.

Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.01/I7

Topic: G.08. Other Psychiatric Disorders

Support: P50 MH096889

Title: Spatial and single cell transcriptomic characterization of the paraventricular thalamus: A node coding salient experiences and adjudicating motivational conflicts

Authors: *M. R. TETZLAFF[1], L. TANIGUCHI[2], C. KOOIKER[3], C. NAGY[4], N. MECHAWAR[5], G. TURECKI[6], T. BARAM[7];
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Montreal, QC, Canada; [6]Dept. of Psychiatry, Douglas Res. Centre, McGill Univ., Montreal, QC, Canada; [7]Anatomy/Neurobiology; Pediatrics, Univ. of California Irvine, Irvine, CA

Abstract: Rationale: The paraventricular nucleus of the thalamus (PVT) is emerging as a brain node of motivational regulation implicated in reward-seeking, arousal, and fear-learning in the context of antecedent early life events. Specifically, we have found the PVT to be implicated in encoding early life adversity (ELA). ELA results in a variety of long-term, sex-dependent cognitive and affective alterations to motivated behaviors in humans and rodents, yet the neural mechanisms of these changes remain unclear. Importantly, fosTRAP methods have shown a robust and specific increased activation of (PVT) cells in pups during the ELA period. However, the role of persistent transcriptomic changes in selective populations of the heterogenous PVT in mediating the effects of ELA on adult motivated behaviors is unknown.
Methods and Results: This ongoing study employs MERFISH spatial transcriptomics and snRNAseq to establish gene expression and spatial organization in the PVT of adult human and mouse with or without a history of ELA. Analyses consider history of ELA, depression in the human and sex across species. We aim to examine potential ELA-induced transcriptomic changes in specific peptidergic cell populations located throughout the PVT, where location governs circuit connectivity. Preliminary results verify that the human, but not mouse, PVT includes inhibitory interneurons, and replicates findings from other groups describing the spatial organization of cell types in the healthy mouse PVT.
Conclusions: This approach may identify mechanisms that translate transient life experiences into enduring functional changes to the PVT and related behaviors, potentially uncovering therapeutic targets. Further, this study will generate the first ever transcriptomic characterization of human PVT cell type and location *and* comparison of human and mouse PVT.

Disclosures: M.R. Tetzlaff: None. **L. Taniguchi:** None. **C. Kooiker:** None. **C. Nagy:** None. **N. Mechawar:** None. **G. Turecki:** None. **T. Baram:** None.

Poster

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Topic: G.08. Other Psychiatric Disorders

Support: MH119456
AG083841

Title: Gabaergic inputs to pomc neurons are modulated by chronic unpredictable stress

Authors: *Y. CHEN[1], X.-Y. LU[2];
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Abstract: We have recently demonstrated that chronic unpredictable stress (CUS) induces hyperactivity of proopiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) and behavioral deficits (Fang, Chen et al., Mol Psychiatry 2021). The hyperactivity of POMC neurons results from both decreased synaptic inhibition and increased intrinsic excitation. Neurons within the dorsomedial hypothalamus (DMH) has emerged as a principal source of inhibitory synaptic inputs to POMC neurons, conveying inhibitory synaptic modulation onto POMC neurons. In this study, we aim to delineate the involvement of GABAergic neurons within the DMH in modulating activity of POMC neurons during chronic stress exposure. Firstly, we recorded the spontaneous firing patterns of GABAergic neurons in the DMH after 10 days of CUS. Our findings revealed a decrease in the spontaneous firing rates of DMH GABAergic neurons following CUS. Subsequently, we investigated the impact of DMH GABAergic neuron activation during chronic stress exposure on the excitability of POMC neurons. Further investigation is underway to elucidate the role of DMH → POMC GABA circuitry in modulating stress-induced behavioral impairments. These investigations will uncover the upstream neurocircuits contributing to POMC neuron hyperactivity and behavioral deficits in the context of chronic stress.

Disclosures: Y. Chen: None. **X. Lu:** None.

Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.03/I9

Topic: G.08. Other Psychiatric Disorders

Title: Binge-eating and obesity induce distinct endocannabinoid system transcriptional regulations in reward-related brain regions

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Abstract: Binge eating disorder (BED) is characterized by the overconsumption of highly palatable food in a short amount of time. BED patients do not display compensatory behaviors such as purging, that could lead to obesity. The endocannabinoid system(ECS) is a biomolecular system involved in palatable food intake and is highly expressed in reward-related brain regions. Recent body of work has shown that ECS is affected in both obesity and BED. However, some discrepancies are reported regarding central dysregulations in these two diseases. Our study aimed to explore potential differences in ECS gene expression between obesity and BED. For this study, male adult Wistar rats were divided into 3 groups: A non-access group (NA) with access only to normal diet, A continuous access group (CA) exposed continuously to a “free choice high fat high sugar” (fcHFHS) diet and modeling obesity, and an intermittent access

group with an intermittent access (IA) to the fcHFHS diet, modeling BED. Food intake was measured daily for six weeks and tissue samples of the nucleus accumbens (NAc), dorsal striatum (DS), ventral tegmental area (VTA) and rostromedial tegmental nucleus (RMTg) were collected to measure mRNA levels of ECS-related genes using qPCR. Continuous and intermittent access to the fcHFHS diet successfully modelized the pattern of eating observed in obesity and BED. Transcriptional analysis shows a reduction of ECS expression in the NAc and RMTg in the CA group while in the IA group, ECS expression was reduced in the dorsal striatum but increased in the RMTg. Furthermore, correlation analysis showed that ECS-related gene expression is differently affected depending on the amount of sucrose or fat consumed. Our findings support the hypothesis that the ECS is differently affected in BED and obesity and indicate that the RMTg could be a region of interest in future studies of these conditions. Furthermore, dysregulation of the ECS seems closely linked with the amount and type of palatable food ingested, supporting the need for additional studies on the differential effects of fat and sugar consumption on the ECS in the reward pathway.

Disclosures: F. Schoukroun: None. **R. Bourdy:** None. **K. Befort:** None.

Poster

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Title: Neural dynamics of updating taste reward expectations

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Abstract: Expectations of reward play a critical role in cognition and decision-making, allowing us to predict the outcomes of certain actions. These expectations can influence which actions we take and also inform how we interpret sensory input. However, when our expectations are wrong, the ability to flexibly shift our behavior in response to unanticipated circumstances is critical for our well-being. For example, recognizing that the milk in the fridge that you thought was still good has actually spoiled protects you from an unfortunate episode of food poisoning. In order to better understand the neural dynamics involved in these processes, I trained monkeys to perform a task in which different image cues predicted the taste of a fluid bolus (from sweet to bitter). Each trial could be either forced-choice (where only one image was presented for

selection) or free-choice (where a choice between two images was presented). In order to select an image, the monkey was required to fixate the image and release a touch-sensitive bar, which was followed by an initial bolus of fluid. Next, there was a four-second period during which each additional response the monkey made on the touch-sensitive bar delivered another, smaller bolus of the same fluid. Monkeys consistently chose sweeter options, and tapped more for them. Once associations were well established, a small percentage of trials became "mismatch" trials, in which the fluid delivered did not match the cue image. On these trials, tapping behavior initially reflected the expected outcome, but shifted over the four-second window in accordance with the actual fluid received. To understand the neural dynamics of expectation in taste perception and motivated behavior, I recorded simultaneously from the orbitofrontal cortex and the gustatory cortex during this task. Previous work has suggested that the activity of the orbitofrontal cortex is flexibly modulated by expectations of taste.

Disclosures: S. McConnell: None. **E.L. Rich:** None.

Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.05/I11

Topic: G.03. Motivation

Title: Cortical functionality in heterosexual men while solving the towers of london during visual erotic stimulation: effects of sexual activation

Authors: *A. FRÍAS DIMAS[1], C. AMEZCUA[2], J. P. GARCÍA HERNÁNDEZ[2], R. M. HIDALGO AGUIRRE[3], M. A. GUEVARA[2];
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Abstract: Sexual activation (SA) generated by visual erotic stimuli is related to an activation of brain areas such as the prefrontal cortex (PFC), parietal (P) and temporal cortex (T), which participate in the detection and processing of stimuli. PFC is also involved in the adequate manifestation of the executive functions. On the other hand, the processing of stimuli with sexual content depends on sexual orientation. The aim of this study was characterized the degree of coupling among PFC, P and T during solving the Towers of London (TOL), after seeing visual erotic stimulation with different content heterosexual video (HEV) and homosexual video (HOV). Fifteen healthy men between 20 and 30 years old participated. The EEG activity of frontal, temporal and parietal areas was recorded while observing of both videos. Participants rated the HEV as pleasant, with higher general and sexual arousal than HOV. Contrary to what was expected, there were no differences in the execution of the TOL between both videos. However, changes in the cortical response did occur. During the TOL execution during HEV, participants presented minor parietal correlation of beta band, associated with the pleasant valence and the global, or contextual, processing of the stimulus with sexual connotation of their

preference, but without interfering with the processing required to adequately execute the cognitive task. According to these results, we can conclude that the SA generated by a video with sexual content, or its characteristics associated with sexual orientation or preference does not impact the cortical functioning for the adequate execution of a cognitive task.

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Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.06/I12

Topic: G.08. Other Psychiatric Disorders

Title: Association between gut microbiota and depressive symptoms in naval personnel with obesity and depression: influence of a weight loss program

Authors: *A. *. FUENTES BELLO[1,2], D. CERQUEDA-GARCÍA[5], A. LUNA[3], C. LANDA-SOLIS[4], M. SAMUDIO-CRUZ[3], P. CARRILLO-MORA[3], E. RANGEL-LOPEZ[6], L. SANCHEZ-CHAPUL[3];
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Abstract: Depression and obesity are conditions with major public health implications. Depression can disrupt the gut-brain axis leading to changes in the composition of gut microbiota (dysbiosis), and these changes may influence neurotransmitter levels and neuroinflammation, contributing to the development or exacerbation of depression. In military personnel, these relationships may be further influenced by a high stress environment; therefore, understanding these interactions will be crucial for developing interventions to promote physical and mental well-being in this population. In this study we aimed to determine the associations between gut microbiota changes and depressive symptoms (without, decreased and increased) after a weight loss program (WLP). We obtained fecal samples of 178 individuals (20 to 65 years) (138 male and 40 female) from the Mexican Navy with obesity, who participated in a WLP (hypocaloric diet and moderated exercise) during 3 months. Biological samples and depression tests were taken at the beginning of the program (basal) and 3 months later. The associations between changes in gut microbiota and depressive symptoms were determined by a generalized linear model with a negative binomial distribution with statistical significance at $p<0.05$. Our result showed that the WLP improved body composition and biochemical parameters. At the beginning of the program, 161(90.5%) had no depressive symptoms and 17 (9.55%) were symptomatic. After 3 months, 148 (83.14%) remained without symptoms, 26 (14.6%) and 4 (2.24%) had

decreased and increased depressive symptoms respectively. The group without changes in depressive symptoms, correlated positively with ASVs (Amplicon Sequences Variants) belonging to genera Prevotella, Alistipes and UCG-005 and negatively with two ASVs of Prevotella, Muribaculaceae, Dialister and Parabacteroides. The group with decreased symptoms positively correlated with Muribaculaceae, Roseburia, Dialister, Prevotella (3 ASVs) and Parabacteroides and negatively with Prevotella, Alistipes, Christensenellaceae, Odoribacter and UCG-005. Finally, the group with increased symptoms had only a negative correlation with 2 ASVs of Prevotella, Muribaculaceae, Coprococcus, Christensenellaceae and UCG-005. We conclude that the diversity of the gut microbiota of our population is similar to that reported for major depressive disorder, and after the 3 months of the WLP, the richness of ASVs of Muribaculaceae, Roseburia, Dialister, Prevotella (4), and Parabacteroides seems to be associated with the reduction of depressive symptoms.

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Poster

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INICI-UV, UVA 2299; and Ideas Mujer 2.0 INGE210003

Title: Effect of inhibiting mesolimbic dopamine neurons on locomotor sensitization to quinpirole and D2 receptor function in mice

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Abstract: The repeated administration of Quinpirole (QNP), a dopamine D2 receptor (D2R) agonist, induces locomotor sensitization, a sustained increase in locomotor activity. Although QNP-induced locomotor sensitization is very robust in rats, this effect is poorly observed in mice. The mesolimbic dopamine system, composed of ventral tegmental (VTA) dopamine neurons projecting to the Nucleus Accumbens (NAc), underlies the induction of locomotor sensitization. QNP activates D2R in medium spiny and dopamine neurons, promoting locomotion and decreasing dopamine release. Previously, we found that rats showing QNP locomotor sensitization have decreased basal dopamine release in the NAc. We hypothesize that the chronic reduction of extracellular dopamine levels facilitates QNP-induced locomotor sensitization. To induce a chronic decrease of NAc dopamine levels independently of D2R activation, we expressed the inhibitory DREADD, hM4Di, selectively in the mesolimbic dopamine pathway in mice and repeatedly administered its agonist C-21. Then, we chronically administered QNP and evaluated locomotor activity after each injection. We found that mice repeatedly treated with QNP did not develop locomotor sensitization. However, QNP administration in C-21 pre-treated mice induced sustained and enhanced locomotion, suggesting that chronic reduction of tonic dopamine in the NAc facilitates QNP-induced locomotor sensitization. Currently, we are setting fast-scan cyclic voltammetry (FSCV) in slices containing the NAc to assess whether the repeated inhibition of mesolimbic dopamine neuron activity impacts D2R presynaptic function, as well as immunofluorescence analysis to evaluate whether this chronic inhibition impacts D2R levels in the VTA and NAc. We intend to contribute to understanding the mechanisms that underlie compulsivity by studying the involvement of D2R in dopamine neurons.

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Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.08/I14

Topic: G.08. Other Psychiatric Disorders

Support: CIHR
Alberta Children's Hospital Research Institute

Title: Perinatal distress in pregnant people during the COVID-19 pandemic and the association with infant brain development and motor outcomes

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Abstract: Maternal mental health is an important predictor of infant and child development. During the COVID-19 pandemic, rates of perinatal maternal depression increased. Previous work has shown that pre and postnatal depression is negatively associated with early neonatal motor abilities. As such, the long-term effects of pre and postnatal depression on the development of child motor abilities and their supporting brain structures for children born during the pandemic should be monitored. The present study had two aims: (1) to examine the effect of pre and postnatal depression and anxiety on the volumes of motor-related brain structures (thalamus, basal ganglia, and cerebellum) in 3-month-old infants born during the COVID-19 pandemic; and (2) to examine whether infant brain volumes at 3 months predict gross motor abilities at 12 months. To address the first aim, data from 91 pregnant participants and their infants (43 female, gestational age at birth=39.6 weeks) were analyzed using multivariate general linear modelling. Perinatal depression and anxiety were measured using the Edinburgh Postnatal Depression Scale (EPDS) and the PROMIS Anxiety Scale, respectively. Of the 91 participants, 21 met criteria for clinically elevated depression and 25 met the criteria for clinically elevated anxiety; 18 had both clinically elevated levels of depression and anxiety). To address the second aim, data from 62 participants and their infants (35 male, 27 female, 12-14 months) were analyzed using generalized linear models. The models were adjusted for infant sex, gestational age at birth, parent age, education, socioeconomic status, total cranial volume, and postnatal psychological distress. Brain volumes were obtained via T1-weighted MRI and automatically segmented using infant Freesurfer. Gross motor abilities were assessed using the Ages and Stages Questionnaire-3. Higher prenatal depressive symptoms were significantly associated with smaller volumes in the right caudate ($p=0.007$), but larger volumes in the right putamen ($p=0.049$) and pallidum ($p=0.014$) at 3 months of age. Higher prenatal anxiety symptoms significantly predicted larger right ($p=0.018$) and left caudate ($p=0.035$) volumes at 3 months of age. Smaller right thalamus volumes at 3 months of age predicted poorer gross motor outcomes at 12 months ($p=0.005$). Differential effects of anxiety and depression were evident in infant brain volumes. The results from this study support the need to monitor the motor abilities of children born during the COVID-19 pandemic on a longer-term basis. These results suggest that perinatal parent mental health can have lasting impacts on child development.

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Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.09/I15

Topic: G.08. Other Psychiatric Disorders

Title: Effect of multiple progesterone withdrawals in female intact rats in experimental anxiety: relevance of stress-vulnerability

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Abstract: Background Preclinical studies on premenstrual anxiety have used a single induction of progesterone withdrawal (PW), that could affect construct validity, as progesterone drop occurs cyclically due to menstrual hormone fluctuations. Moreover, stress susceptibility plays an important role in developing Premenstrual mood disorders (PMDs). Thus, it is crucial to have an animal model that represents the stress vulnerability observed in PMDs suffering people and strengthens homological validity. Therefore, we evaluated the response of a stress-vulnerable strain, the Wistar-Kyoto rats (WKY), to multiple PW on experimental anxiety.
Method Wistar (control strain) and WKY (stress-vulnerable strain) rats were used. PW consisted of administering 2mg/kg of progesterone during 5 consecutive days with a 48h washout period, until completion of 3 cycles of PW. Twenty-four hours after the last progesterone administration, animals were tested in the elevated-plus maze, light-dark test and open field test. Behavioral assessments occurred in every PW cycle.
Results PW increased anxiety-like behavior in WKY rats evaluated on the EPM by reducing the % of time in open arms and increased grooming behavior at PW1 ($p<0.05$). A similar pattern was observed in the open field test, and an increase in grooming behavior was observed in at PW3 only in WKY. Of interest, the light-dark test was ineffective in detecting significant changes in WKY rats, while only anxiogenic effect was observed in Wistar rats at PW2 ($p<0.05$).
Conclusion The anxiogenic-like effect of PW was observed depending on the rat strain evaluated. Stress vulnerability could increase susceptibility to anxiety-like behavior induced by PW. These results constitute a preclinical approximation to evaluate anxiety related to PMDs with stronger construct validity, as cyclicity is simulated and differs from other animal models with longer progesterone exposures used to simulate postpartum depression. The potential effect of re-exposure to behavioral assessments cannot be disregarded.

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Poster

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Topic: G.08. Other Psychiatric Disorders

Support: NIH R01 NS112176
NS129549
R42NS125895

Title: Accurate modeling of dopamine release kinetics: comparison and validation of kinetic models using fast scan cyclic voltammetry

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Abstract: Dopamine is a neurotransmitter present within the mammalian brain that is responsible for a wide range of physiologic functions, including incentive motivation, reward, and movement control. Changes or dysfunction in the dynamics of dopamine release is thought to play a pivotal role in regulating various physiological and behavioral processes, as well as leading to neuropsychiatric diseases. Therefore, it is of fundamental interest to neuroscientists to understand and accurately model the kinetics that govern dopaminergic neurotransmission. In the past several decades, many mathematical models have been proposed to capture the biologic parameters that govern dopaminergic kinetics, with each model seeking to improve upon a previous model. In this study, each of these models are derived, and the ability of each model to properly fit six fast scan cyclic voltammetry (FSCV) datasets will be presented. The models were divided into single-compartment models (1: First order release-reuptake and 2: Diffusion gap) and multi-compartment models (3: Restricted diffusion, 4: Modified restricted-diffusion, 5: Modified restricted-diffusion with hang-up correction, 6: Three compartment, and 7: Three compartment with hang-up correction). The dopamine oxidation current in all FSCV datasets exhibits hang-up and overshoot behaviors, which have traditionally been difficult for mathematical models to capture. While no single model is clearly the best, models should be selected based on their mathematical properties to best fit the FSCV data one is trying to model. Here, we show that an added hang up correction to current models greatly improves their ability to represent dopamine release that exhibits these behaviors. The modified restricted diffusion model with hang-up correction performed better than the more complex three compartment model, including all other models. Models such as these can be utilized to explore how changes in synaptic parameters, neural activity, or external stimuli can impact dopamine release kinetics, and how changes in these kinetics are correlated with phenotypic or behavioral changes in the organism.
Overall, developing such differential equation models to describe the kinetics of dopamine release from the synapse confers significant applications, both for advancing scientific understanding of dopamine neurotransmission, as well as for advancing clinical ability to treat neuropsychiatric diseases. In addition, the model's predictive capabilities may guide the optimization of drug treatments and aid in the design of novel therapeutic strategies, ushering in a new era of precision medicine in neurology and psychiatry.

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Poster

PSTR130: Motivation

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Topic: G.08. Other Psychiatric Disorders

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Pritzker Neuropsychiatric Disorders Research Consortium
Grinnell College Center for Careers Life and Service

Title: Effect of chronic stress on whole blood transcriptome in mice: a systematic meta-analysis of publicly available transcriptional profiling datasets

Authors: *E. I. M. FLANDREAU[1], M. H. HAGENAUER[2], T. DUAN[4], A. BADER[4], S. J. WATSON, Jr.[5], H. AKIL[3];
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Abstract: Stress increases the risk for psychiatric disorders and animal models of stress-induced biological changes are important tools in translational research. However, successful translation is impeded by small sample size and lack of directly comparable cross-species measurements. As a meta-analysis, the present study addresses the issue of power. As an accessible tissue, blood allows direct comparison between mouse models and human subjects.Blood microarray and RNA-Seq datasets from rodent studies were systematically identified in Gemma, an open-source database of curated and re-analyzed transcriptional profiling studies. Three microarray datasets (GSE68076, GSE72262, and GSE84185) derived from whole blood samples met inclusion/exclusion parameters. Each study exposed eight-week old mice to chronic stress (5 or 10 days social defeat stress, 6 weeks chronic mild stress, or 8 weeks unpredictable chronic mild stress, respectively). When necessary, we subsetted to the relevant tissue (whole blood) and removed outlier samples and genes lacking variability. The final sample size was n=92 (n=45 Non-Stress/n=47 Stress: GSE68076: n=17/19 male C57Bl6 mice (1 outlier per condition eliminated), GSE72262: n=12/12 female C57Bl6/j mice, GSE84185: n=16/16 male Balb/c mice). Differential expression related to chronic stress in each dataset was quantified using the Limma pipeline followed by empirical Bayes moderation. Differential expression results were aligned across datasets by mouse Entrez Gene ID. For genes included in all three studies, we ran a meta-analysis of Log2FC values (with accompanying sampling variance) using a random effects model, and corrected for false discovery rate (FDR). Functional patterns in results were assessed with fast Gene Set Enrichment Analysis using the Brain.GMT (v.2) gene set database.Of 9,219 commonly identified genes, 23 transcripts were downregulated and 16 upregulated in stress-exposed mice (FDR<0.05). Enrichment analysis identified down-regulation in gene sets related to leukocytes, lymphocytes, T cells, B cells, and immune function, DNA/chromatin regulation, RNA processing and translation, cellular metabolic processes, and mitochondrial function and

organelles. Upregulated gene sets related to erythrocytes and oxygen binding, synapses, cell junctions, transport, and cell signaling. Our results implicate specific genes and pathways in the widespread immune dysregulation observed following chronic stress and identify stress-induced changes in whole blood transcriptome as a potential tool for improved translation across species.

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Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.12/I18

Topic: G.08. Other Psychiatric Disorders

Support: ZIAMH002927

Title: The Impact of Intravenous Ketamine Treatment on Sleep and Suicidality

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Abstract: Insomnia is a risk factor for suicide, and sleep disruption is associated with increased risk for death by suicide. Ketamine (0.5 mg/kg) is associated with reductions in depression, suicidal thoughts, and improved sleep. It is important to understand the physiological changes that may lead to ketamine's anti-suicidal effects to learn who would most benefit. We aimed to evaluate self-reported sleep across the continuum of suicide risk and ketamine's impact on sleep and suicidal ideation in those with a recent suicide crisis. We hypothesized individuals with a recent suicide crisis would have increased PSQ-I global sleep scores, majority report sleep difficulties preceding a suicide crisis, and ketamine would reduce insomnia symptoms and suicidal ideation. Participants were recruited into a neurobiology of suicide study and categorized into 1 of 4 groups: 1) experienced a suicide crisis within two weeks (High-Risk (HR), n=14), 2) experienced a suicide crisis more than a year ago (Low-Risk (LR), n=41), 3) presence of any psychiatric diagnosis without a history of suicide (Clinical-Controls (CC)) (n=39), 4) healthy volunteers (HV) (n=32). Participants completed the Pittsburgh Sleep Quality-Index (PSQ-I) to measure self-reported sleep over the last month. HR and LR participated in a retrospective reporting of clinical symptoms around suicide attempt interview (RRSA) to evaluate sleep the night prior to their suicide crisis. A subsample of HR received in-patient ketamine (n=9) and completed the Hamilton Depression Rating Scale at baseline and 1-day post-ketamine. One way ANOVA evaluated group differences in the PSQ-I global scores and post-

hoc tests compared HR, LR, CC, and HV. The RRSA was analyzed descriptively. A paired t test assessed ketamine changes in insomnia and suicide items on the HAMD. There were group differences in the PSQ-I ($F(3,118)=29.59$, $p<.001$): post-hoc tests highlighted HR, LR, and CC were significantly increased compared to HV ($p<0.005$). HR had an increased trend in global PSQ-I scores compared to LR ($p=0.057$). On the RRSA, 77% of HR and LR reported sleep problems the night before their suicide crisis; specifically, 54% reported difficulty falling asleep. Ketamine significantly reduced suicidal thoughts ($t_{df=8}=2.8$, $p<0.05$) and insomnia in the middle of the night ($t_{df=8}=2.53$, $p<0.05$). This study adds to the literature by focusing on the impact of ketamine on sleep in an at-risk sample. The findings underscore sleep disruptions as a potential risk factor for a suicide crisis and the potential for ketamine to improve suicidal thoughts and sleep. Future studies should explore the effects of interventions on suicide related sleep measures.

Disclosures: A. Tillman: A. Employment/Salary (full or part-time):; National Institutes of Health. **D. Greenstein:** A. Employment/Salary (full or part-time):; National Institutes of Health. **N. Hejazi:** A. Employment/Salary (full or part-time):; National Institutes of Health. **L. Waldman:** A. Employment/Salary (full or part-time):; National Institutes of Health. **C.A. Zarate:** A. Employment/Salary (full or part-time):; National Institutes of Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application for ketamine in depression. **E. Ballard:** A. Employment/Salary (full or part-time):; National Institutes of Health.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.13/I19

Topic: G.03. Motivation

Support: ERC Grant No. 852189

Title: The relation between low-grade inflammation and effort-based food decisions in overweight and obesity

Authors: *J. M. SCHOLING, R. VAN DEN BOSCH, E. AARTS;
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Abstract: Obesity is a major health problem worldwide and is typically driven by increased intake of high-caloric, easily available foods. Such altered effortful food choice behavior may be partially explained by increased inflammation levels that are prevalent in obesity. Outside the field of obesity, increased inflammation has been associated with loss of motivation and decreased effortful behavior. Here, we investigated how low-grade inflammation is related to effortful food-choice behavior in overweight and obesity. In this cross-sectional study, we included 120 18-59-year-old women with a body mass index (BMI) >27 kg/m^2. Low-grade

inflammation was assessed from C-reactive protein (CRP). Participants performed an effort-based decision-making task, in which they were presented with a series of offers to work for food items. On each trial participants decided whether they were willing to exert a certain amount of effort (squeeze handgrip device; 4 levels calibrated to max strength) for food rewards that varied in quantity (1 vs 4 items) and caloric content (high vs low). We used multilevel binomial regression to test whether acceptance rates of the offers depended on (the interaction between) CRP, effort, reward quantity, and reward calories. Participants accepted fewer offers when higher effort was required (Odds Ratio (OR): 0.01, 95% Confidence Interval (CI): 0.00, 0.02, $p<0.001$) and accepted more offers when more reward was offered (OR: 7.32, 95% CI: 4.22, 8.58, $p<0.001$), but there was no main effect of caloric content (OR: 0.83, 95% CI: 0.43, 1.22, $p=0.534$). We found that CRP was associated with higher acceptance rates for high caloric food (OR: 1.75, 95% CI: 1.04, 2.97, $p=0.036$). In addition, CRP was marginally associated with lower acceptance rates for higher effort levels (OR 0.64, 95% CI: 0.38, 1.07, $p=0.095$) and with higher acceptance rates for more reward (OR 1.38, 95% CI: 0.97, 1.95, $p=0.075$). However, all associations with CRP disappeared after the model was adjusted for BMI (all $p>0.1$). These findings show that, independent of BMI, CRP is not associated with food-related effort-based decision making in overweight and obesity. Future work should dissociate the role of CRP from BMI using a broader inflammatory profile and interventional designs.

Disclosures: J.M. Scholing: None. **R. Van Den Bosch:** None. **E. Aarts:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

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Program #/Poster #: PSTR130.14/I20

Topic: G.08. Other Psychiatric Disorders

Title: The effectiveness of neurofeedback and brain-computer interface training for the treatment of ADHD: A meta-analysis

Authors: *A. M. CROOM, S. DETHOMASIS, M. NAJM, O. NASSIM, D. O'DEA;
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in children with a prevalence of 8.7% (or 5,300,000 children) in the United States (Bozinovic et al.2021). ADHD negatively impacts the lives of individuals and societies, with those diagnosed showing a 12% reduction in employment, 34% reduction in earnings, twice the rate of attempted suicide, and six times the rate of suicide completion compared to typically developing individuals (Faraone et al. 2021). Therefore, conducting systematic research and developing effective treatments for ADHD is of growing importance, and recently, scholars have investigated the possibility of using neurofeedback (NFB) training through game-based brain-computer interfaces (BCIs) as a possible non-pharmacological treatment for ADHD. But is NFB-BCI training an effective non-pharmacological treatment for

ADHD? If so, how effective is NFB-BCI training at reducing ADHD symptoms, such as inattention? To provide answers to these important questions, we followed PRISMA guidelines and conducted a systematic literature review and meta-analysis on all randomized controlled trials (RCTs) that compared the effectiveness of NFB-BCI training versus different controls (waitlist, placebo) on ADHD symptoms (such as inattention). Using a random effects model, we found a large effect for the use of NFB-BCI training vs waitlisted controls on the reduction of ADHD symptoms ($k = 10$, SMD = -0.85, $p = 0.028$). Yet we found no statistically significant effect for the use of NFB-BCI vs placebo controls ($k = 4$, SMD = 0.15, $p = 0.344$). Here we discuss the results of our research on NFB-BCI training for ADHD treatment as well as methodological issues with current placebo controlled studies (Pigott, Cannon & Trullinger 2018). Here we also discuss the practical value and limitations of this research along with prospects for future work.

Disclosures: A.M. Croom: None. **S. DeThomasis:** None. **M. Najm:** None. **O. Nassim:** None. **D. O'Dea:** None.

Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.15/I21

Topic: G.08. Other Psychiatric Disorders

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Dr. Albert C. Yang was supported by he Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Spectral analysis of polysomnography for insomnia disorder using machine learning approaches

Authors: *W.-Y. HUANG[1,2], A. C. YANG[2,3,4,5];
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Taiwan; [4]Brain Res. Ctr., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [5]Dept. of Med. Res., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Background: With the advent of data mining and artificial intelligence (AI), the large data of polysomnography can be more easily analyzed to discern differences between insomnia and normal sleep patterns. Machine learning (ML) techniques can identify key features, potentially serving as markers for diagnosing insomnia disorder (ID). The objective of this study was to construct ML models that accurately distinguish individuals with ID from good sleepers (GS) using power spectral features in each sleep stage, and to examine the disease-related impacts on sleep stages and specific frequencies. **Methods:** A total of 100 participants were included in the study, comprising 50 individuals with ID and 50 GS. All subjects underwent one-night polysomnography. EEG epochs from frontal recordings were extracted from the same sleep stage to create five stage-specific datasets: wake, rapid eye movement (REM) sleep, and non-rapid eye movement (NREM) sleep stages 1 to 3. The normalized power spectra of the epochs within each sleep stage, ranging from frequencies of 0.03 to 50 Hz, were utilized as features. A sampling rate of 200 Hz and 30-second epochs yielded a total of 1,500 power spectral features for training purposes. Each dataset was divided into an 80% training set for training on an online commercial AI platform (AI-PaaS), which provides a variety of algorithms. During training, hold-out cross-validation was conducted. A variety of machine learning models were employed for ensemble learning, with the remaining 20% of the dataset designated for testing purposes. **Results:** The results of the accuracy tests revealed that the most effective model for classifying ID was developed for the NREM2 stage at the F3 channel, achieving an accuracy of 81.83% using the Light Gradient Boosting Machine (LightGBM) classifier. Models trained on NREM2 data exhibited higher classification accuracies compared to other sleep stages, indicating a more significant impact of insomnia on the NREM2 stage. The LightGBM classifiers exhibited superior performance compared to other algorithms in the ensemble trials. Regarding model explainability, the EEG frequencies at 30 Hz were found to demonstrate the most dominant discriminative ability throughout the entire night. **Conclusion:** Our findings indicate that spectral features can be used to accurately categorize ID. Insomnia appears to have a substantial impact on high beta to low gamma oscillations throughout the night. These findings represent a progression in our comprehension of the pathophysiology of insomnia and its implications for objective ID evaluation.

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Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.16/I22

Topic: H.03. Decision Making

Title: Effect of a stressor on the relationship cortisol - brain activity in decision making

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Abstract: Stress is a set of reactions that tend to restore homeostasis of the body when a stimulus is perceived as a threat (stressor). Exposure to a stressor is associated with physiological changes that include an increase in cortisol concentration and changes in the functionality of different brain areas, such as the prefrontal and temporal cortex, which present specific activity during cognitive processes such as decision-making (DM). It has been reported that DM changes depending on cortisol levels, and cortisol levels in turn affect electroencephalographic (EEG) activity. Based on the above, the objective of this study was to determine the relationship between cortisol concentration and EEG activity during DM in the presence of a stressor. Twenty healthy, right-handed men between the ages of 20 and 35 voluntarily participated in the study and solved a DM task with (n=10) and without (n=10) exposure to a stressor with the objective of accumulating as many points as possible. The absolute power (AP) of the frontopolar cortex (Fp1-Fp2), the dorsolateral cortex (F3-F4), the temporal cortex (T3-T4), and the correlation (r) between cortisol and the AP were analyzed. No differences were found in the performance of the DM task between groups. The analysis of the relationship between the concentration of cortisol and the AP of the different regions indicated a positive relationship for the group with stressor rFp1 [theta: r= 0.66 p(r)≤ 0.04; alfa1: r= 0.59 p(r)≤ 0.07; alfa2: r= 0.65 p≤0.04], rFp2 [theta: r= 0.68 p(r)≤ 0.02; alfa2: r= 0.62 p≤0.05], rF3 [alfa2: r= 0.66 p≤0.03], rF4 [theta: r= 0.67 p(r)≤ 0.03; alfa1: r= 0.62 p(r)≤ 0.05], rT3 [alfa1: r= 0.61 p(r)≤ 0.05; alfa2: r= 0.68 p≤0.02; beta1: r= 0.82 p(r)≤ 0.01] while the relationship between variables is almost null in most areas for the group without stressor. Regarding the comparison of correlations between the group with and without exposure to the stressor, differences were found in the Fp1-Fp2, F3-F4, and T3. In the presence of a stressor during DM, there is a positive correlation between the level of cortisol and the AP of some EEG bands in cortical areas such as prefrontal and temporal areas. That is, the higher the level of cortisol, the higher the AP. It is likely that this change in correlation is associated with a functional neuromodulation mechanism, necessary to adequately execute the DM task.

Disclosures: F. Iribe Burgos: None. **C. López Esparza:** None. **J.P. García Hernández:** None. **P. Cortes Esparza:** None. **M. Hernandez:** None. **M.A. Guevara:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.17/I23

Topic: G.04. Emotion

Support: National Institutes of Health (R01MH124687, R01NS120851)
the Minnesota Medical Discovery Team on Addictions

Title: Cognitive Control-Informed Deep Brain Stimulation programming optimization in Psychiatric Disorders

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Abstract: After surgery, precise programming of deep brain stimulation (DBS) targeting the ventral capsule/ventral striatum (VCVS) is crucial for maximizing treatment effectiveness. Our recent study has shown the potential to replace the current subjective trial-and-error method of DBS programming for psychiatric disorders. We proposed an online closed-loop framework utilizing reaction time, measured through the Multi Source Interference Task, as an objective marker of cognitive control. Systematically investigating various electrode contacts, we aimed to identify those significantly improving cognitive control using Bayesian optimization algorithms. By implementing the Upper Confidence Bound (UCB1) algorithm over multiple days and selecting the optimal stimulation site using majority voting, an approximate accuracy of 80% for 8 stimulation sites can be achieved. Building upon these results, we extend this study by aggregating reaction times (RT) from multiple days and analyzing the combined data using a generalized linear mixed model to identify optimal stimulation sites. Furthermore, we propose integrating additional DBS parameters—specifically, frequency, and pulse width—within the state space formulation (SSM) and adopting a multi-parameter optimization approach. Given the absence of a definitive ground truth for individual parameter effects, we outline a comprehensive strategy, including leveraging existing rodent data to approximate the impacts of various parameters and creating a data generator that closely mimics practical outcomes. To assess the effectiveness of this approach, we plan to employ Gaussian process regression and Bayesian optimizers with a diverse set of acquisition functions and evaluate their ability to retrieve known ground truth. This methodology, which has demonstrated success in movement disorders, holds significant implications for the field of neuromodulation in psychiatry. By providing an in-silico version of a real-time closed-loop system, this research could potentially cut down patient care costs and accelerate the time for patients to benefit from treatment.

Disclosures: S. Nagrale: None. **A. Yousefi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); unlicensed intellectual property in the area of brain stimulation optimization, including patent applications related to the subject of this poster. **T.I. Netoff:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); unlicensed intellectual property in the area of brain stimulation optimization, including patent applications related to the subject of this poster. **A.S. Widge:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); unlicensed intellectual property in the area of brain stimulation optimization, including patent applications related to the subject of this poster..

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.18/I24

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Mk-801 reverses anxiety and depressive-like behaviors caused by progesterone withdrawal in wistar kyoto

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Abstract: Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome. Women who suffer from PMDD presents symptoms related to anxiety and depression, and exposure to stress increases susceptibility to the development of PMDD. Among the causes of PMDD is the abrupt drop in progesterone levels during the luteal phase of the menstrual cycle, coupled with increased sensivity to the effects of estrogen and progesterone, a poor regulation of HPA axis and changes in GABA sensitivity. Pharmacological treatments are intermitent and focus mainly on the relief of the physical and psycological symptoms inherent to PMDD through the suppression of ovulation or with antidepressant drugs. Nevertheless, at moment a non-effective treatment to PMDD symptoms exist and recently it has been proposed an imbalance between GABA and glutamate in this pathology. Non-competitive NMDA receptor antagonists, such as MK-801, induce rapid antidepressant effects in different animal models of depression, even under conditions of hyperreactivity to stress. However, it has not yet been evaluated whether these drugs improve symtoms derived from PMDD. Therefore, the main goal of this work was to evaluate the anxiolytic and antidepressant-like effect of MK-801 under condition of progesterone withdrawal (PMDD model) in vulnerable strain to stress (Wistar Kyoto). Thus, independent groups of female Wistar Kyoto rats (WKY) were administered progesterone for five days. On the sixth day, MK-801 was administered. Subsequently, animals were evaluated in the open field (OF), forced swimming test (FST) and Defensive Burying Behavior Test (BBT) to elucidate if MK-801 improved anxiety and depression-like behaviors induced by preogesterone withdrawal (PW). PW induces an increase in immobility (depression-like behavior) in FST and burying time in BBT (anxiety-like behavior), without affecting locomotor activity in the open field. MK-801 reverses the effect of PW in FST, increasing swimming, therefore MK-801 may activate serotinergic neurotransmission. In the BBT the burying time is reduced with administration of MK-801, without changes in locomotor activity. In conclusion, MK-801 was able to prevent the anxiety and depression-like behavior generated by progesterone withdrawal in WKY rats.

Disclosures: J. Chan monroy: None. **C. Lopez-Rubalcava:** None. **E.M. Estrada:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.19/I25

Topic: H.03. Decision Making

Support: University of Illinois internal grant

Title: Anxiety predicts everyday decision outcomes beyond general intelligence

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Abstract: Prior research has demonstrated a strong relationship between higher general intelligence (*g*) and greater decision-making competence (Barbey, 2019), suggesting that problem-solving strategies applicable to lab-based tests can be adapted to solve everyday problems. Mental health issues like anxiety have separately been implicated in reducing the quality of decisions (Hartley & Phelps, 2012). However, it remains unclear whether anxiety exerts its effect on decision outcomes more by disrupting the application of strategies underlying general intelligence, or through independent pathways like motivation and emotion regulation (Bruine de Bruin et al., 2020). To fill this gap, we administered as part of an ultra-high field fMRI study a standard battery of general intelligence tests (Wechsler Adult Intelligence Scale-IV; Lichtenberger & Kaufman, 2012), a comprehensive psychological symptom inventory (Symptoms Checklist-90-Revised; Derogatis & Savitz, 1999) and a representative survey of everyday decision outcomes (Decision Outcome Inventory; Parker et al., 2015) to a sample of 47 subjects recruited from the University of Illinois campus in Urbana. We replicated the strong positive association between *g* and decision-making competence reported by Barbey (2019; r=.54; p<.001). Our results also extend Hartley and Phelps's (2012) reported negative relationship between anxiety and lab-focused decision-making tasks by demonstrating a strong correlation between higher anxiety and lower ability to competently solve everyday problems (r=-0.38; p=.005). Both *g* and anxiety remained significant predictors of decision making competence in a regression analysis (*g*: F=15.76; p<.001; Anxiety: F=8.79; p=.005) but showed no significant interaction (p=.36). This suggests the pathways through which anxiety and *g* influence everyday decision-making are largely independent. We discuss the implications for studying problem-solving in the lab versus the real world as well as ongoing analyses to identify the structural and functional underpinnings of the two pathways.

Disclosures: V. Patel: None. **B. Hemmatian:** None. **A.K. Barbey:** None. **R. wilcox:** None. **L. Varshney:** None. **J. Wu:** None.

Poster

PSTR130: Motivation

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Program #/Poster #: PSTR130.20/I26

Topic: H.03. Decision Making

Support: FAPESP Grant 2017/16473-6
CAPES
CNPq

Title: Top-down projections of the prefrontal cortex to state-setting monoaminergic and cholinergic nuclei in the mid- and hindbrain

Authors: R. A. DE SOUZA[1], L. GONCALVES[2], ***M. METZGER**[1];
[1]Dept. of Physiol. & Biophysics, Univ. of Sao Paulo, Inst. of Biomed. Sci., Sao Paulo, Brazil;
[2]Dept. of Human Anat., Federal Univ. of the Triangulo Mineiro, Uberaba, Brazil

Abstract: Anatomical and functional evidence suggests that the prefrontal cortex (PFC) is fairly unique among all cortical regions, as it not only receives input from, but also robustly projects back to mesopontine monoaminergic and cholinergic cell groups. Thus, the PFC is in position to exert a powerful top-down control over several state setting modulatory transmitter systems that are critically involved in the domains of arousal, motivation, reward/aversion, working memory, mood regulation, and stress processing. Regarding this scenario, the origin of cortical afferents to the ventral tegmental area (VTA), laterodorsal tegmental nucleus (LDTg), as well as the dorsal (DR) and median raphe nucleus (MnR) was here compared in adult male rats, which received single iontophoretic injections of the retrograde tracer cholera toxin subunit b (CTb). CTb labeling in these cases was revealed by single immunoperoxidase techniques. We also investigated the collateralization of prefrontal afferents to the DR and VTA by coincident injections of Fluorogold into VTA and CTb into DR. In these cases, we applied multiple immunofluorescence labeling protocols for visualization. Single CTb injections into VTA, LDTg, DR or MnR produced retrograde labeling in the cortical mantle, which was mostly confined to frontal polar, medial, orbital, and lateral PFC subdivisions, along with anterior- and mid-cingulate areas. Remarkably, in all of the four groups, retrograde labeling was densest in layer V pyramidal neurons of the infralimbic, prelimbic, medial/ventral orbital and frontal polar cortex. Moreover, a lambda-shaped region around the apex of the rostral pole of the nucleus accumbens stood out as heavily labeled, mainly after injections into the lateral VTA and LDTg. In general, retrograde PFC labeling was strongest following injections into MnR and weakest following injections into DR. Double imunofluorescence labeling revealed that almost half of the DR-projecting neurons also project to the VTA, whereas only about 10% of VTA-projecting neurons simultaneously innervate the DR. Altogether, our findings reveal a fairly similar set of prefrontal afferents to VTA, LDTg, DR, and MnR, further supporting an eminent functional role of the PFC as a controller of major state setting mesopontine modulatory transmitter systems. Moreover, our findings highlight that single PFC cells, particularly DR-projecting neurons, target both DR and VTA, expanding our anatomical knowledge about how the PFC can modulate and synchronize activity in the DR and VTA.

Disclosures: R.A. De Souza: None. **L. Goncalves:** None. **M. Metzger:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.21/I27

Topic: G.01. Fear and Aversive Learning and Memory

Title: Efficacy of style of reappraisal on fear extinction and recall

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Abstract: Extinction could be considered a bottom-up approach to regulate fear responses. However, in some cases, it may result in a relapse of fear. This deficit demands a strategy that could reinforce extinction. The current study aimed to investigate the top-down regulatory processes like cognitive reappraisal on fear extinction and fear recall augmentation. We used the screaming lady fear conditioning paradigm with 63 participants (M=43, F=20) (Mean age = 20.6, SD= 1.40) and fear and expectancy ratings as outcome measures. The participants were randomly divided into three groups: Creative reappraisal (CR; n=23), Ordinary reappraisal (OR; n=21) and Standard extinction only (SE; n=19) group. The creative and ordinary reappraisals used in the current experiment were generated by a few students and the experimenter respectively. We followed a three-day design with habituation and acquisition on day 1, extinction on day 2 and extinction recall on day 3. A one-way ANOVA result revealed a significant group difference on differential fear ratings during extinction [$F(2,62) = .112$, $p = .05$] with the OR group indicating lower fear ratings than CR group. In extinction recall phase the groups differed significantly on differential fear ratings [$F(2,62) = 3.902$, $p = .026$]. We found a trend level significant difference between OR and CR group and a significant difference between OR and SE group. It is proposed that using CR with extinction trials may hamper extinction learning, however, from our results we found that CR although aimed at reducing the aversiveness of the UCS does not disrupt prediction error. A rmANOVA of early and late trials of extinction expectancy ratings showed that there was a significant main effect of extinction trial type [$F(1,60) = 33.011$, $p < .001$, $\eta p2 = .355$] with higher expectancy ratings in early trials implying higher initial prediction error. There was no significant extinction trial type x group interaction effect, this result indicates that all the three groups underwent comparable extinction. Our results imply a superior effect of OR in attenuation of recall of fear responses, it hints that nature of reappraisal plays a role in reduction of fear responses. Factors like believability of reappraisal, matching the context, such factors are related to implementation cost of reappraisals. It appears that CR results in a higher implementation cost hence less effective in reducing fear responses. Further, targeting UCS aversiveness through reappraisal does not inhibit extinction. These results might aid with interventions for anxiety disorders using cognitive reappraisal.

Disclosures: K. Dar: None. **M.K. Asthana:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.22/I28

Topic: H.08. Learning and Memory

Support: BBRF NARSAD Grant 30176

Title: Reward-predictive cue favors automaticity, habit and preference in a choice setting

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Abstract: Adaptive decision-making requires to choose the best option among different alternatives and to select appropriate responses efficiently, which can be achieved through habit learning. Choice and habit are generally considered as countervailing processes, mainly because making choices is assumed to involve goal-directed control in order to compare available options and select the most appropriate one, based on the expected value of each option. However, previous studies have shown that a choice can be habitual (Vandaele et al, 2019, 2020, 2022). Yet, the relation between habit and preference remains unclear. In this study, we developed a new procedure to investigate habit in a choice setting and to determine how habit relates to preference. More specifically, we trained rats to choose between two rewards (equicaloric solutions of sucrose and maltodextrin), and we promoted habit for one reward specifically, by signaling its delivery with a cue, while delivery of the alternative reward was not signaled by the cue. We found that presentation of the reward-predictive cue favored automaticity, habit and preference for the signaled reward, specifically. In contrast, responding for the alternative unpredicted reward was under goal-directed control. This new procedure allows direct comparison of habitual and goal-directed responding within the same session and is thus, relevant to investigate the neurobiological bases of habitual preference in a choice setting.

Disclosures: Y. Vandaele: None. **N. Thiriet:** None. **M. Solinas:** None.

Poster

PSTR130: Motivation

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Topic: H.03. Decision Making

Support: NIMH #R21MH127607
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University of Minnesota's MnDRIVE (Minnesota's Discovery, Research and Innovation Economy) initiative.

Title: Deciphering Neural Mechanisms of Explore-Exploit Decision-Making in the Prefrontal Cortex

Authors: *X. YAN[1], S. KOENIG[2], B. EBITZ[3], B. Y. HAYDEN[4], D. P. DARROW[5], A. B. HERMAN[5];
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Abstract: Successful navigation in unfamiliar environments requires individuals to strike a balance between exploration and exploitation, a fundamental aspect of foraging behavior. Deciphering the neural underpinnings of these decision-making processes is crucial for understanding adaptive behaviors. In this study, we investigated human explore-exploit decision-making using a three-armed bandit task and recorded intracranial EEG data from the ventral medial prefrontal cortex (vmPFC), dorsal medial prefrontal cortex (dmPFC), and dorsolateral prefrontal cortex (dlPFC) in 14 epilepsy patients. By fitting behavior to a reinforcement learning foraging model (RL-foraging model), we identified distinct roles of these prefrontal regions in value computation and action execution. Specifically, neural oscillations (4-14 Hz) in vmPFC and dmPFC were implicated in value computation, while dlPFC showed engagement during action execution. Moreover, dlPFC and dmPFC encoded unsigned prediction error (PE), whereas vmPFC selectively tracked negative PE. Connectivity analyses revealed that only the connection between dmPFC and dlPFC reliably predicted subsequent trial behaviors. Transfer entropy analysis further demonstrated that dmPFC conveyed information to dlPFC during the feedback stage, influencing decision-making in the subsequent choice stage. Our findings illuminate the differential contributions of vmPFC, dmPFC, and dlPFC to explore-exploit decision-making and underscore the pivotal role of dmPFC-dlPFC interaction in guiding final decisions. These findings contribute to the broader field of decision neuroscience and shed light on the neural basis of adaptive behaviors in uncertain environments.

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Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.24/I30

Topic: H.03. Decision Making

Title: Neural substrates underlying overcoming automatic behavioral tendencies in approach-avoidance conflict decisions

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Abstract: Adequate control over automatic behavioral responses to affective stimuli is crucial for adaptive goal-oriented behaviors. However, it is unclear how individuals override motivational approach-avoidance behaviors in response to appetitive and aversive stimuli. Thus, we combined a previously developed free versus forced approach-avoidance conflict decision task with brain imaging (fMRI) to identify neural substrates underlying the control of automatic behavioral tendencies. Before the AAC task, participants underwent short acquisition training to associate specific conditioned stimuli (CSs) with either an aversive (avCS+) or appetitive (appCS+) outcome, both outcomes (confCS+), or no outcome (neuCS-). In the AAC task, CSs were presented in an anticipation phase to capture decision-making processes, followed by a response period, where participants could either approach and obtain CS-specific outcome or avoid without getting anything. In Free trials, both approach and avoidance options are available, while only one option is available in forced trials. Response times, subjective ratings of valence and arousal, electrocardiogram, eye-tracking, and functional imaging data were recorded. Preliminary results showed that CSs were differentially evaluated. Participants exhibited faster preferential responses to stimuli associated with a single outcome (e.g., avoidance to the avCS+), but slower reactions when forced to perform the opposite responses (e.g., approach to the avCS+), which is expected to be related to greater activation of the prefrontal cortex. Conflicting outcomes modestly facilitated the overriding processes, indicated by reduced response times for forced decisions. This is expected to be associated with lower activation in the dorsal anterior cingulate cortex during the response phase. It may provide insights for the development of clinical interventions targeting psychopathologies such as anxiety and addiction disorders.

Disclosures: M. Chen: None. **A. Pittig:** None. **M. Gamer:** None.

Poster

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Topic: H.03. Decision Making

Support: NIH EB T32 EB025816
NIH NCATS KL2TR002381
NIH NCATS UL1TR002378
Julian T. Hightower Chair
Georgia Institute of Technology

Title: Anterior cingulate dynamics during effortful walking in humans

Authors: *T. D. ALBARRAN[1], C. MAY[1], K. HERRIN[2], J. LEESTMA[2], T. HARVEY[2], A. YOUNG[2], G. SAWICKI[2], C. ROZELL[1], S. ALAGAPAN[1];
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Abstract: Interoception, or the monitoring of the internal state, is a critical system that is impaired in many brain disorders such as depression, anxiety, and Parkinson's disease. Energy regulation, or the homeostatic balance between energy expenditure and food intake, is an important component of interoception. While the brain circuits underlying energy regulation are not fully understood, the anterior cingulate cortex (ACC) has been shown to play an important role, with animal studies showing that the ACC encodes representations of physical effort [1]. However, it remains unclear whether the ACC tracks energy expenditure in humans.
In this study, we recruited 10 healthy volunteers to explore how changes in energy expenditure, induced by walking at different incline levels, relate to ACC dynamics. Using a 64-channel EEG system (ANT Neuro, PA, USA) and a mobile indirect calorimetry unit (COSMED, GA, USA) to measure neural activity and metabolic output, participants completed two 6-minute treadmill walking trials for each incline: 0° (low-effort) and 6° (high-effort). EEG data were preprocessed and decomposed into independent components using EEGLAB, which were source-localized with DIPFIT. Each recording session contained one primary dipole source (RV < 5%) localized to the ACC, which was then converted into the canonical frequency band signals.
Preliminary analysis of 3 participants revealed distinct increases in high-beta (20-30 Hz) ACC band power (6.03 +/- 3.87 % dB, N=3) during incline walking. We also observed that ACC high-beta activity increases (slope = 3.69e-3 +/- 5.13e-3 dB/min, N=6) over high-effort trials, whereas it decreases during low-effort trials (slope = -2.82e-3 +/- 1.03e-3 dB/min, N=6).
Participants had an 83.47 +/- 13.66 % (N=6) increase in kcal/hr between the high- and low-effort trials, which is potentially encoded by these high-beta dynamics. Our preliminary findings provide support that the ACC not only holds representations of physical effort in humans but that the representation changes with sustained effortful action.
1. Porter BS, Hillman KL, Bilkey DK. Anterior cingulate cortex encoding of effortful behavior. J Neurophysiol. 2019 Feb 1;121(2):701-714. doi: 10.1152/jn.00654.2018. Epub 2019 Jan 9. PMID: 30625016.

Disclosures: T.D. Albarran: None. **C. May:** None. **K. Herrin:** None. **J. Leestma:** None. **T. Harvey:** None. **A. Young:** None. **G. Sawicki:** None. **C. Rozell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest in Motif Neurotech, Inc. F. Consulting Fees (e.g., advisory boards); advisory board. **S. Alagapan:** None.

Poster

PSTR130: Motivation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.26/I32

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH/NIMH Grant R01MH132018-02
NSF Grant IOS 2137023

Title: Neural encoding of valencies in the BNST-CeA-DRN circuits, and the implications for stress-linked behavioral responses.

Authors: *I. E. LIM, O. M. OGUNDELE;
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Abstract: Neural circuits containing projections from the dorsal raphe nucleus (DRN), bed nucleus of the stria terminalis (BNST), and central amygdala (CeA) govern the expression of psychosocial states, anxiety, and other related behaviors. How these circuits contribute to the expression of anxiogenic behaviors primarily driven by aversive stimuli has been tested with great certainty. However, the role of this circuit (triad) in the expression of behaviors that discriminate between positive and negatively valenced stimuli is still poorly understood. This study deploys multi-site high throughput *in vivo* recording methods, with chemogenetics, to investigate the encoding mechanism of this circuit when positive and negatively valenced stimuli are presented. To anatomically ascertain and map the composition of this circuit, anterograde (AAV-hSyn-DIO-mcherry and AAV-hSyn-DIO-eYFP) and retrograde tracers (rhodamine and fluorogold) were injected bilaterally, and counterstained with neuron-specific cell markers. Specifically, cells labeled retrogradely or anterogradely were co-localized with glutamate, GABA, tryptophan hydroxylase (serotonin), and corticotrophin-releasing hormone (CRH). Electrophysiological profiles (ground truth) of glutamate, GABA, serotonergic, and CRH neurons in the circuit were also determined by photostimulation (AAV-DIO-hChR2-eYFP) in *Vglut2*^{cre}, *Vgat*^{cre}, *Sert*^{cre}, and *Crh*^{cre} mice. In head-fixed anesthetized mice (7 males and 7 females), the response of putative cells in the DRN, CeA, and BNST was assessed by firing rate analysis when ethologically relevant odorants were presented to produce positive or negative contexts. The results demonstrate sex-specific complementary and opposite firing rate patterns in the BNST and DRN - but not in the CeA - in response to an acute stressor. The neural connectivity patterns were altered in a sex-linked manner in response to different thresholds of an acute stressor, confirming the role of this circuit in stress-related responses. To elucidate the role of DRN serotonergic neurons and their terminals in modulating BNST and CeA neuronal ensembles, we injected AAV-hSyn-DIO-hM4D(Gi)-mcherry and AAV-hSyn-DIO hM3D(Gq)-mcherry in the DRN of two separate cohorts of animals. We expect unique encoding and regulatory mechanisms from the modulation of DRN 5-HT terminals that innervates CRH neurons in the BNST and CeA axis. In conclusion, the results demonstrate basal sex-linked sensitivity of the triad to both positive and negative valenced stimuli. Furthermore, the encoding and regulatory mechanisms will discriminate between valences of stimuli by altering the magnitude of FR change.

Disclosures: I.E. Lim: None. **O.M. Ogundele:** None.

Poster

PSTR130: Motivation

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR130.27/I33

Topic: H.03. Decision Making

Support: CIHR 20R77768
NSERC 20R76081

Title: Changes in anterior cingulate cortex (ACC) neural dynamics and dopamine levels as rats prepare for a forthcoming challenge

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Abstract: A main function of the ACC is monitoring and regulation of autonomic states. Not only is this view consistent with the anatomy of ACC circuits, but also with decades of research showing that stimulation of the ACC modulates autonomic arousal in lab animals and evokes a sense of rising to a forthcoming challenge in awake human subjects (Parvizi et al 2013). We sought to understand the underlying neural mechanisms by recording from the ACC as rats performed a variable effort task. The task was performed on a treadmill and involved signalling the required running speed of an upcoming higher-intensity 'interval' (HII) through a tone (the frequency of tone correlated with treadmill speed in the upcoming interval). Three different speeds of HIIs were used within a session that were adjusted throughout the experiment so that difficulty was maintained as best as possible for each rat. Rats received a reward if they successfully managed to complete a trial, and failed a trial if they hit a shock grid at the end of the treadmill more than three times. Since the tone preceded the HII by 5s, we could analyze ACC activity as the rats mentally prepared for an upcoming challenge. Dopamine (DA) responses were also measured using fiber photometry in combination with the fluorescent DA sensors Dlight2.1 or GrabDA3h. Tetrode-based recordings showed that ACC neurons exhibited unique ensemble states during the preparatory tone periods that preceded different HIIs. ACC DA levels also increased during this period before plateauing as the speed of the treadmill stabilised at the final speed for the HII. Differences in DA responses were evident on failed versus completed trials. These experiments will provide insights into how ensemble dynamics and changes in DA levels in the ACC help the body prepare for difficult forthcoming efforts.

Disclosures: A. Lindsay: None. **E. Croy:** None. **I. Gallello:** None. **J.K. Seamans:** None.

Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.01/I34

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R00 AA024208
NIH Grant R01 AA029130
NIH Grant T32 AA026577

Title: Chronic ethanol exposure produces long-lasting, subregion-specific physiological adaptations in RMTg-projecting mPFC neurons

Authors: *K. R. PRZYBYSZ, E. J. GLOVER;
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Abstract: Chronic ethanol exposure produces neuroadaptations in the medial prefrontal cortex (mPFC) that contribute to the maladaptive behaviors associated with alcohol dependence and interfere with recovery from alcohol use disorder. The majority of research supporting this is limited to studies of the prelimbic subdivision of the mPFC (PL mPFC), despite strong evidence that the infralimbic subdivision (IL mPFC) also plays a key role in addiction. While much of this work is limited to assessments of individual subregions, recent data suggest that discrete cortical circuits play distinct roles in behavior. The rostromedial tegmental nucleus (RMTg) is involved in aversive signaling and is functionally altered by chronic ethanol exposure. Notably, the RMTg receives dense input from both the PL and IL mPFC. However, the effects of chronic ethanol exposure on these circuits are unknown. The present study addressed this gap by investigating the lasting physiological changes resulting from chronic ethanol exposure in RMTg-projecting PL and IL mPFC neurons. Adult male Long-Evans rats were injected with fluorescent retrobeads into the RMTg and rendered ethanol dependent using a standard 14-day chronic intermittent ethanol (CIE) vapor exposure paradigm. Whole-cell patch-clamp electrophysiology was performed on fluorescently-labeled (RMTg-projecting) and -unlabeled (projection-undefined) layer 5 pyramidal neurons 7-10 days following ethanol exposure. We observed an increase in intrinsic excitability ($p=0.02$) in RMTg-projecting, but not projection-undefined, IL mPFC neurons. CIE exposure also increased excitatory and inhibitory synaptic drive in a manner that was specific to RMTg-projecting IL mPFC neurons ($p<0.05$). In contrast, CIE exposure had no lasting effects on the excitability of RMTg-projecting PL mPFC neurons, although a significant CIE-induced reduction in excitability was observed in projection-undefined PL mPFC neurons ($p=0.02$). CIE exposure also increased excitatory synaptic drive in RMTg-projecting PL mPFC neurons ($p<0.05$). Together, these data reveal novel subregion- and circuit-specific neuroadaptations in the mPFC following chronic ethanol exposure. These results highlight the unique vulnerability of the IL mPFC-RMTg circuit to the physiological effects of chronic ethanol. Future research linking these neuroadaptations with ethanol-induced changes in mPFC-dependent behavior will be key for advancing our understanding of how changes in neural circuit function impede recovery from alcohol use disorder.

Disclosures: K.R. Przybysz: None. **E.J. Glover:** None.

Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.02/I35

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH NIAAA grant R01 AA029130
NIH NIAAA grant P50 AA022538

Title: Effects of chronic ethanol exposure on mPFC calcium activity associated with appetitive and aversive salience processing and behavioral responding

Authors: *S. HOU, E. J. GLOVER;
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Abstract: Reward prediction error (RPE) is a computational neural process that compares outcomes with expectations to guide decision making and adaptive responding. Disrupted RPE signaling underlies impaired decision making, a consequence consistently observed in alcohol use disorder (AUD). The medial prefrontal cortex (mPFC) plays a critical role in decision making and emerging data suggests that distinct mPFC cell populations encode RPE. However, the effect of chronic ethanol exposure on RPE processing in the mPFC is unknown. Adult male and female Long-Evans rats were classically conditioned to associate an audiovisual cue with delivery of either a sucrose pellet or foot shock. In vivo fiber photometry was used to measure GCaMP7s, an indicator of intracellular calcium activity, in the prelimbic (PL) subregion of the mPFC during learning and in response to expected and unexpected outcomes. Rats were subsequently rendered dependent using a standard 14-d chronic intermittent ethanol (CIE) vapor exposure paradigm. Controls were exposed to room air (AIR). One week after their last vapor exposure, rats resumed behavioral testing to determine the effect of CIE on behavioral responding and PL calcium signal. Before CIE, PL mPFC calcium signal increased significantly from baseline in response to both appetitive and aversive cues ($^*p<0.0001$). In contrast, opposing changes in calcium signal were observed in response to outcomes with a significant decrease from baseline in response to appetitive outcomes ($^*p<0.01$) and an increase in response to aversive outcomes ($^*p<0.0001$). Calcium signal did not reflect trial-by-trial changes in expected outcome for appetitive or aversive stimuli across learning or RPE probe sessions. However, it was significantly negatively modulated by reward seeking in the appetitive task ($^*p<0.001$) and positively modulated by active threat responses in the aversive task ($^*p<0.0001$). In AIR controls but not in CIE-exposed rats ($^*p<0.01$), we observed attenuation of the appetitive cue-induced increase in calcium signal over time. In contrast, CIE exposure significantly attenuated the aversive cue-induced increase in calcium signal relative to AIR controls ($^*p<0.0001$). In addition, CIE disrupted the relationship between threat responding and PL calcium signal. Altogether, these results indicate that bulk PL mPFC calcium activity does not encode RPE, but instead reflects a combined signal integrating the salience of environmental stimuli and behavioral responding to those stimuli. Our data further suggest that impaired mPFC engagement during salience processing occurs in a valence-specific manner following chronic ethanol exposure.

Disclosures: S. Hou: None. **E.J. Glover:** None.

Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.03/I36

Topic: G.09. Drugs of Abuse and Addiction

Support: R01 AA031003
P50 AA022538
T32 AA02657

Title: Withdrawal-induced changes in LHb excitability and RMTg astrocyte morphology

Authors: *K. BOSQUE CORDERO[1], E. J. GLOVER[2];
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Abstract: Alcohol Use Disorder (AUD) involves persistent excessive drinking despite adverse effects. Around 50% of those with AUD suffer from withdrawal symptoms, triggering relapse. The rostromedial tegmental nucleus (RMTg) signals aversion, and its function is implicated in withdrawal symptoms. The lateral habenula (LHb) provides dense glutamatergic input to the RMTg and parallels its function, including involvement in withdrawal symptoms. However, the exact mechanisms by which the LHb and RMTg regulate these symptoms remain unclear. Chronic ethanol exposure alters astrocyte density and morphology, impacting synaptic transmission due to astrocytes' role in modulating neuronal activity at tripartite synapses. To assess the effects of withdrawal from chronic ethanol on RMTg and LHb astrocytes, Long-Evans rats underwent chronic intermittent ethanol (CIE) vapor exposure for 14 hours/day for 14 days. Acute withdrawal from CIE was associated with a significant increase in the expression of the astrocytic marker, glial fibrillary acidic protein (GFAP), in the RMTg compared to AIR controls (*$p < 0.05$; nested t-test). This effect was primarily driven by greater GFAP expression at rostral levels of the RMTg in CIE- relative to AIR-exposed rats (*$p < 0.05$). GFAP expression was also greater in the LHb of CIE-exposed rats compared to AIR controls although this effect did not reach statistical significance. In a separate group of rats, we found that CIE exposure produced a significant reduction in the excitability of LHb neurons, which was accompanied by a significant increase in interspike interval (*$p < 0.05$; unpaired t-test). Ongoing experiments are exploring how CIE-induced changes in astrocytic clearance of glutamate from the synapse may contribute to this effect. Altogether, these data shed light on the effects of chronic ethanol exposure on LHb and RMTg physiology and astrocyte morphology providing potential insight into the ways in which these brain regions regulate withdrawal symptoms.

Disclosures: K. Bosque Cordero: None. **E.J. Glover:** None.

Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.04/I37

Topic: G.09. Drugs of Abuse and Addiction

Support: NHRMC Synergy Grant RG214234

Title: Effects of FGF21 analogue PF-05231023 on alcohol drinking and conditioned approach behaviours.

Authors: *B. J. COOLEY, W. A. HELLER, A. LIM, C. OCCELLI HANBURY-BROWN, G. P. MCNALLY, Z. MILLAN;
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Abstract: Rationale. Fibroblast growth factor 21 (FGF21) is a liver-derived hormone that reduces alcohol consumption in mice and non-human primates. However, the role of FGF21 in regulating other alcohol-related behaviours is unknown. **Objectives.** Here we sought to test the effect of a long-acting analogue of FGF21, PF-05231023 on established intermittent home cage drinking in mice as well as to investigate the impact of PF-05231023 on Pavlovian conditioned approach to alcohol and sucrose cues. **Methods.** In Experiment 1, the effects of i.p 1mg/kg, 3mg/kg and 10mg/kg of PF-05231023 were tested on ethanol consumption of C57BL/6J mice with a history intermittent ethanol access using a within-subjects latin-square design. In Experiment 2, the 3mg/kg effective dose of PF was tested on 8% and 15% ethanol conditioned approach behaviours. In Experiment 3 we validated a within-subjects conditioned approach protocol and confirmed the conditioned reinforcing properties of 15% ethanol and sucrose cues. We then assessed the effect of 3mg/kg and 10mg/kg of PF treatment on 15% ethanol and sucrose conditioned approach behaviours. **Results.** In Experiment 1, PF-05231023 reduced alcohol consumption and preference in a dose- and sex-dependent manner. In Experiment 2, PF-05231023 attenuated alcohol Pavlovian conditioned approach behaviours in a sex-dependent manner. Finally, in Experiment 3, PF-05231023 impaired approach behaviours in a dose and outcome selective manner. **Conclusions**. These findings show that PF-05231023 can attenuate established alcohol drinking behaviours and indicate sex and dose-dependent treatment effect(s) on alcohol related conditioned approach behaviours.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.05/I38

Topic: G.09. Drugs of Abuse and Addiction

Title: The Role of Insula Activity During Drinking and Negative Affect-like Behavior

Authors: *T. ADKINS, J. LITTLE, S. CENTANNI;
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Abstract: Alcohol use disorder (AUD) presents with individualistic variability leading to challenges in diagnoses and therapeutic treatments. Neurocircuits provide insight into the mechanisms necessary for encoding complex behaviors. Previous studies have investigated the motivation of alcohol consumption while delineating the characteristics of drinking behavior before and after alcohol exposure paradigms. Yet, little has been uncovered regarding neurocircuitry *during* drinking behavior. The mid-insula is involved in motivation, substance use disorder, and stress behaviors. Characterizing neural activity in the insula during drinking could provide insight into the progression from casual alcohol use to AUD in certain individuals. In our search to learn more about the neural mechanisms that drive drinking behavior, we investigate neural activity in the insula during drinking. Using a modified Drinking in the Dark (DID) model paired with *in vivo* GCaMP fiber photometry we identified time-locked increases in mid-insula GCaMP at the onset of a lick. We hypothesized a reflective increase in mid-insula GCaMP during negative affect-like behavior in protracted abstinence. To test this, we investigated negative affective behavior and calcium release during protracted abstinence using the novelty suppressed feeding test (NSFT), startle response (acoustic, foot shock, and air puff), elevated plus maze, and light-dark paradigms. All behaviors were paired with fiber photometry to assess the insula activity relationship with behavioral responses. Increased acoustic and foot shock startle responses were seen along with an increase in calcium activity during air puff and foot shock startle in the EtOH exposed group. Interestingly, startle behaviors were not reflective of neural activity suggesting the potential role of insular circuits in negative affective behaviors. Given the breadth of inputs and outputs to the insula, current studies are investigating whether specific insula projections will provide more information regarding this dissonance.These experiments lend insight into the real-time activity occurring at the onset of a lick increasing our knowledge of the insula during drinking. Further understanding of these roles will provide potential targets for the treatment of AUD and other co-morbid disorders.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: Research Society for Alcohol Doctoral Student Small Grant Award
WSU Alcohol and Drug Abuse Program Graduate Research Grant
NIAAA R01 AA02078-01

Title: Selectively targeting cerebellar adaptations during withdrawal reduces alcohol withdrawal severity

Authors: *N. A. MCLEAN[1], S. N. SHIPPELL STILES[2], A. E. HARDER[2], G. J. LEE[2], D. J. ROSSI[3];
[1]Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA; [2]Washington State Univ., Pullman, WA; [3]Integrative Physiol. & Neurosci., Washington State Univ., Pullman, WA

Abstract: Alcohol Use Disorder (AUD) is a complex disorder that can be broken down into binge intoxication, withdrawal, and preoccupation stages, each with their own unique symptomology which require specialized treatment options. During chronic alcohol (EtOH) consumption, homeostatic neuroadaptations occur, which in the absence of EtOH result in aversive withdrawal symptoms that collectively drive renewed EtOH consumption to alleviate such symptoms. Importantly, the cerebellum is exceptionally sensitive to acute EtOH and while known for its role in motor impairment, there is an increasing appreciation for the role of the cerebellum in more emotional and cognitive functions, such as addiction. However, the roles of the cerebellum in the context of chronic EtOH exposure and withdrawal are not well understood. Here, we determine how the cerebellum adapts to chronic EtOH exposure, if the onset of withdrawal symptoms correlates with development of cerebellar neuroadaptations, and if the cerebellum can be used as a selective target for the treatment of EtOH withdrawal symptoms. Using patch-clamp recording in *ex vivo* brain slices, we recorded from cerebellar granule cells (GCs) of EtOH withdrawn mice and determined that withdrawal from chronic EtOH causes a decrease in GC inhibitory tone, comprised of a decrease in sIPSC frequency and a reduction of tonic $GABA_A$ receptor current. The severity of this adaptation is contingent on the duration of EtOH exposure, with no significant changes in GC inhibitory tone after 24 hours, a strong decreasing trend after 48 hours, and a significant decrease after 72 hours of EtOH exposure. Concurrent with these neuroadaptations, EtOH withdrawn mice have a shorter time to fall on the accelerating rotorod and elicit more low frequency ultrasonic vocalizations than their air exposed counterparts, which are indicative of motor impairment and negative emotionality, respectively. Importantly, during EtOH withdrawal, chemogenetic inhibition of GCs via activation of Gi-coupled DREADDs selectively expressed in GCs improves rotorod performance compared to heterozygous controls. Collectively, these results indicate that GC inhibitory tone is reduced during withdrawal from chronic EtOH exposure along with the onset of behavioral withdrawal symptoms, and selectively restoring GC inhibitory tone during EtOH withdrawal lessens the severity of aversive withdrawal symptoms, highlighting the cerebellum as a promising pharmacotherapeutic target for treating the withdrawal stage of the AUD cycle.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

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Program #/Poster #: PSTR131.07/I40

Topic: G.09. Drugs of Abuse and Addiction

Support: R01AA027213
P50DA044123
U01NS115587

Title: Neural Signatures of Aversion-Resistant Ethanol Seeking in the Anterior Insula

Authors: *A. LAWRENCE[1], S. JUNG[2], S. KOUKUNTLA[3], A. CHENG[3], A. R. GRAVES[1], S. P. MYSORE[4,1], T. HARRIS[6], P. H. JANAK[4,1,5];
[1]Neurosci., Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Univ., BALTIMORE, MD; [3]Biomed. Engin., [4]Psychological and Brain Sci., [5]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD; [6]Biomed. Engin., HHMI JRC, Ashburn, MD

Abstract: Drug seeking and intake despite adverse consequences is a central aspect of addictive behavior. Like human addicts, a subset of rats continues to self-administer drugs despite the presence of an aversive stimulus such as electric shock or a bitter tastant, quinine, mixed in the drug solution. The anterior insula (aIC), a central mediator of interoception and motivation is postulated to play a role in both drug-seeking and evaluation of aversive states, and therefore may be a critical mediator of drug seeking despite adverse consequences. To examine aIC neural activity in real-time under such conditions, we recorded ~3800 single and multi-units from the aIC in four (2 females and 2 males) freely-moving Long Evans rats chronically-implanted with neuropixel 2.0 probes while they performed an ethanol-reinforced instrumental task. Rats were trained on a discrete trial instrumental task in which each trial began with lever insertion and responding on the lever resulted in lever retraction and ethanol (EtOH; 10% w/v) delivery (0.16 mL/trial). EtOH sessions were followed by quinine-adulterated EtOH sessions to model reward-seeking and intake under conflict. We obtained recordings during 5-7 sessions per week over 2-4 weeks per rat. Neural activity was sorted using Kilosort 2.5 followed by manual curation. Analysis of neural activity dynamics at lever insertion, a highly salient cue signaling opportunity to access EtOH reward, revealed modulation of cue-elicted activity of single-units by motivation to respond and by the presence of quinine, when comparing EtOH-only sessions with EtOH-quinine sessions during which rats continued to respond for and consume the reward. Large proportions of the neural population showed cue-modulated activity (20-35%/session; Wilcoxon signed ranksum test, $p<0.05$). During rewarded trials, the z-scored firing rate of significantly cue-excited neurons increased, and the z-scored firing rate of significantly cue-inhibited neurons decreased in EtOH-quinine compared to EtOH-only sessions (Wilcoxon ranksum test, $p<0.05$). At the neuronal population level, we observed a higher modulation in at least one of the top three principal components at lever insertion during EtOH-quinine compared to EtOH-only sessions, and abrupt transitions in activity states on omitted trials. These results indicate that the aIC is differentially recruited during aversion-resistant and non-aversion-resistant EtOH seeking, with stronger neural encoding of the reward cue when subjects continue to seek EtOH despite the presence of an aversive stimulus, supporting the hypothesis that the aIC is a critical mediator of drug seeking under conflict.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR131.08/J1

Topic: G.09. Drugs of Abuse and Addiction

Support: FAPESP
AFIP
NIH

Title: Effects of acute or chronic alcohol exposure on neuronal activity of the dorsal striatum subregions and its afferent targets: globus pallidus and substantia nigra

Authors: *S. MATOS MENDES FERREIRA BADARO[1,2], T. CARNEIRO[3], K. ABRAHAO[3];
[1]NIH/NIAAA, Rockville, MD; [2]Universidade Federal de Sao Paulo, Sao Paulo, Brazil; [3]Univ. Federal de Sao Paulo, Sao Paulo, Brazil

Abstract: The Basal Ganglia comprise subcortical brain regions crucial for motor-control, learning and decision-making. The striatum (Str), the primary input nucleus of the basal ganglia, contains sub-regions such as the rostral (ROS), dorsomedial (DMS), dorsolateral (DLS) and tail (TAIL) portions, pivotal for alcohol abuse goal-directed behavior or habit formation. The Str neurons send GABAergic projections to the external globus pallidus (GPe) and substantia nigra pars reticulata (SNr). While studies have focused on alcohol's effects on Str neuronal activity, less attention has been given to GPe and SNr. Thus, we determined the pattern of neuronal activation of the Str, GPe and SNr following ethanol administration using c-Fos immunostaining, a proto-oncogene that is expressed in neurons after depolarization. Adult male C57BL/6 mice (8 weeks) were distributed into three treatment groups: saline (SS, n = 5), acute (SE, n = 7), and chronic (EE, n = 5) ethanol exposure. Animals received daily intraperitoneal (i.p.) injections of either saline (SS and SE groups) or ethanol (2 g/kg; 15% w/v) (EE group) for 11 days and a final injection, on day 12, of saline (SS group) or ethanol (SE and EE groups). Ninety minutes after the last i.p. administration, mice were perfused and had their brains removed and processed for c-Fos immunofluorescence. Images were taken using a confocal microscope, and c-Fos staining was analyzed by counting immunopositively nuclei with a semi-automated method developed using the ImageJ software. Our results indicate that c-Fos expression in the Str is reduced after acute and chronic ethanol administration when compared to animals in the saline group. When analyzing each Str subregion, the c-Fos reduction was observed among ROS, DMS and DLS regions but not in TAIL. Additionally preliminary data indicate a reduction in neuronal activity in GPe (n = 2-4), but not in the SNr (n = 1-2). Further analysis will investigate the GPe and SNr anatomical subregions too. As expected, ethanol exposure leads to dumped neuronal activation in different subregions of the Basal Ganglia. Our results suggest that the striatal (especially the subregions ROS, DMS and DLS) pallidal pathways (either the indirect pathway or the direct pathway collaterals) may be particularly affected by ethanol exposure.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Program #/Poster #: PSTR131.09/J2

Topic: G.09. Drugs of Abuse and Addiction

Support: R01AA028218 (J.R.B.)
F31AA031427 (B.A.C)

Title: Changing effects in PACAP system function during the transition to ethanol dependence

Authors: *B. A. CARPENTER[1], J. MAZZERINA[1], M. C. JENNINGS[1], A. HAWKS[1], J. R. BARSON[2];
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Abstract: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a stress-related neuropeptide that is highly expressed in the paraventricular thalamus (PVT), a midline thalamic limbic region that participates in ethanol drinking. Our laboratory has recently shown that PACAP over-expression in the PVT is sufficient to reduce ethanol intake in non-dependent animals. A feature of stress-related neuropeptides, however, is that they can become dysregulated with the transition to dependence, and shift from inhibiting to promoting ethanol intake. In this study, we investigated the effects of activity in cells of the PVT and also PACAP in the PVT on ethanol intake, and how these effects change with the development of ethanol dependence. We injected both wildtype and transgenic PACAP-Cre (Adcyap1-2A-Cre) mice with excitatory (AAV8-hSyn-hM3D-mCherry for wildtype; pAAV8-hSyn-DIO-hM3D-mCherry for transgenic) or control (AAV-hSyn-mCherry for wildtype; pAAV8-hSyn-DIO-mCherry for transgenic) DREADDs in the PVT and then gave them access to 20% ethanol on an intermittent access, two-bottle choice (IA) procedure for 4 weeks. We then induced ethanol dependence or maintained non-dependent drinking by exposing animals for 4 weeks to chronic intermittent ethanol (CIE) vapor or air (n = 8/group/sex/virus). After this, we injected animals within-subject with the DREADD activator CNO or saline vehicle (IP) and monitored their subsequent IA drinking. We found that activation in non-dependent and dependent mice had different effects on IA ethanol intake, showcasing a shift in function in the PACAP system during the transition to dependence. Next, in light of the dense PACAP projections from the PVT to the nucleus accumbens (NAc), we explored the mechanism behind this shift in the effects of PACAP by examining gene expression of the PAC1 receptor in the NAc. We trained wildtype mice to drink on the IA procedure before exposing them to CIE or air (n = 8 group/sex), or we maintained them on water and chow alone (n = 8/sex). Using quantitative real time-PCR, we found that both ethanol drinking and ethanol dependence led to significant changes in expression of variants of

the PAC1 receptor. These results suggest that dysregulation of the PACAP system is involved in the development of ethanol dependence. Further understanding of this change could allow for future individualized treatment options.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Program #/Poster #: PSTR131.10/J3

Topic: G.09. Drugs of Abuse and Addiction

Support: AA029970

Title: Regulation of amygdala and dopamine system in naïve and chronic alcohol states

Authors: *C. LAPISH[1], A. S. KUZNETSOV[2];
[1]Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Mathematical Sci. and Ctr. for Mathematical Biosci., Indiana Univ. Indianapolis, Indianapolis, IN

Abstract: Alcohol Use Disorder (AUD) is characterized by a critical shift where negative emotions and cravings intensify, driving cycles of binge/intoxication, withdrawal, and preoccupation. While dopamine (DA) system is classically implicated in addictions, this involvement of emotional dysregulation suggests a contribution of the amygdala as well. This study investigates interaction of DA system and amygdala in AUD. Specifically, we create a computational model simulating activity levels and interactions of basolateral amygdala (BLA), bed nucleus of the strial terminals (BNST) and the ventral tegmental area (VTA). The nuclei are involved in a feedback loop of interactions reproduced in the model. The model accounts for alterations of the connectivity among and inputs to specific neural groups after chronic alcohol exposure. Our results show that the BLA-BNST-VTA feedback loop combines the control of the emotional state together with alcohol drinking (and appetitive behavior in general). Specifically, we have found that chronic alcohol exposure alters the loop to lower the background DA levels and amplify DA transients in response to alcohol-associated cues. Furthermore, our simulations show that, after chronic alcohol, DA transients may transition from biphasic to strictly positive. This transition may signify an elevated alcohol seeking and drinking after chronic alcohol exposure. Finally, our model demonstrates a mechanism that bidirectionally connects fear or stress with predisposition to alcohol seeking and consumption. On one hand, our model suggests that weaker activation of the BLA-BNST-VTA feedback loop contributes to heightened anxiety via a reduction in BLA DA levels after chronic alcohol drinking. On the other hand, it shows how stress primes the agent to escalate alcohol use. Understanding this interaction is crucial for developing treatments preventing AUD progression.

Disclosures: C. Lapish: None. **A.S. Kuznetsov:** None.

Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

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P50 DA033945/DA/NIDA NIH HHS/United States
AA027989/AA/NIAAA NIH HHS/United States
U54 AA027989/AA/NIAAA NIH HHS/United States

Title: Stress-induced escalation of alcohol consumption and limbic microglial dynamics in male and female C57BL/6J mice

Authors: *Y. MINEUR[1], A. R. SOARES[2], V. J. GARCIA-RIVAS[3], M. A. THOMAS[4], C. FAI[5], X. ZHENG[5], M. PICCIOTTO[6];
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Abstract: Despite the escalating prevalence of alcohol use disorder (AUD), particularly among women in recent years, clinical investigations often neglect sex-specific distinctions. As documented in human studies, preclinical data suggest that stress amplifies alcohol intake in females; yet, a comprehensive understanding of sex-specific neurobiological substrates underlying this phenomenon is only emerging. Microglia, the resident macrophages of the brain, are essential to reshaping neuronal processes and contribute to overall neuronal plasticity, as observed in response to stress and chronic alcohol use. We therefore investigated the interactions of stress and alcohol on microglial dynamics and morphology, particularly within limbic structures implicated in addictive processes. In a modified paradigm of intermittent binge drinking (repeated “drinking in the dark”), we determined that female mice were prone to increased stress-induced alcohol consumption after the presentation of repeated foot shocks. Ethanol (EtOH) exerted a variety of anti-inflammatory effects on microglia in the limbic system (amygdala and hippocampus), many of which were more pronounced in females. The results were complicated by interactions between stress and EtOH, which are antagonistic in some cases and synergistic in others, and microglial dynamics were therefore sex-, stress-, and brain region-specific. We therefore used the CSF1R antagonist PLX3397 to deplete microglia in females. We observed an unforeseen reversal of stress-induced binge drinking, highlighting a complex role for microglia in alcohol use, neuronal plasticity, and stress disorders specific to women. These findings accentuate the imperative of integrating sex-specific considerations into the refinement of tailored interventions for AUD.

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Chronic intermittent ethanol effects on dorsal striatal cholinergic signaling

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Abstract: Alcohol use disorder (AUD) is a prevalent issue in the United States, with over 29.5 million people fitting the criteria for the disorder in 2021. Alcohol misuse has adverse health and socioeconomic impacts totaling over $240 billion annually in the United States. Despite this, FDA approved medications for AUD are limited. Thus, further understanding of neurobiological mechanisms underlying AUD is required for the development of new treatments. The neurotransmitter acetylcholine (ACh) plays a role in cognition and decision-making processes, both of which are adversely affected in AUD making it an attractive pharmacotherapeutic target. Therefore, this study aimed to determine how chronic ethanol affects ACh signaling in the dorsal striatum (DS). We previously reported the effects of ethanol on striatal ACh release by performing brain slice photometry using iAChSnFR, a biosensor that increases fluorescence intensity upon binding ACh. We used stereotaxic injection of AAVs to express iAChSnFR in DS of C57BL6J mice. We previously showed that mice which underwent chronic intermittent ethanol (CIE) vapor exposure, a model of ethanol dependence, led to a deficit in dorsal striatal ACh release. To determine what underlies the DS ACh release deficit we examined if CIE treatment adversely affected cholinergic interneurons (CINs), the principal source of DS ACh and the pedunculopontine nucleus (PPN) which accounts for a small percent of DS ACh. We used immunohistochemistry (IHC) and performed stereological counting of dorsal striatal CINs in control and CIE mice. The CIE treatment group underwent ethanol vapor exposure for 16 hours per day, for four consecutive days, followed by 72 hours of withdrawal. This cycle was repeated for four weeks. Post CIE treatment, mice brains were perfused, and 40um-thick coronal sections were prepared for immunofluorescent staining with a choline acetyltransferase antibody (ChAT) to label ACh producing neurons. Stereological counting of striatal CINs resulted in a

deficit of CINs in the dorsomedial striatum (DMS) but not the dorsolateral striatum (DLS) for our CIE group compared to controls. Re-examination of our iAChSnFR data with respect to DS subregions revealed a trend towards loss of CINs in the DMS but not DLS, mirroring our cell count data. Stereological counting of PPN cholinergic neurons (CNs) for CIE and control groups resulted in no significant treatment effect. We also performed stereological counts of the nucleus accumbens, nucleus basalis of meynert, diagonal band, and the medial septal nucleus, all major cholinergic nuclei. Across these brain regions, cholinergic neuron numbers were unaffected by CIE treatment.

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Poster

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NIH Grant R21 AA029498
BEPE FAPESP Award - Process number 2022/10168-5

Title: The effect of KOR antagonists on stress-induces relapse, drinking and irritability of post-dependent CIE rats

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Abstract: Chronic alcohol use leads to long-term counteradaptations in the brain. These adaptations, which manifest as negative emotional symptoms and sleep disturbances during abstinence and motivate relapse through negative reinforcement, are thought to relate to neuropharmacological plasticity in stress-related circuits, including kappa opioid receptors (KOR). The present study tested the hypothesis that systemic administration of a KOR antagonist would reduce stress-induced reinstatement of ethanol-seeking or post-dependent drinking and that these effects would be greater in subjects that showed greater sleep disturbance or irritability during acute withdrawal. Wistar rats (n=46) received 6 weeks of 30-minute fixed-ratio-1 ethanol self-administration sessions followed by 6 weeks of chronic intermittent ethanol (CIE) vapor exposure. During acute withdrawal in the CIE phase, the severity of physical withdrawal, sleep disturbance, and irritability were measured. Rats then underwent 2 weeks of extinction and abstinence, followed by pretreatment with CYM-53052 (KOR antagonist) before variable

footshock-induced reinstatement testing. After establishing stable voluntary intake over 2 weeks, the effects of CYM-53052 on post-dependent 2-bottle choice drinking were then compared with or without pre-session exposure to an empty, ethanol-scented bottle. The results show that CYM-53052 (30 mg/kg) significantly reduced voluntary ethanol intake and preference in male, but not female, rats and had a greater effect in reducing ethanol intake in subjects with fewer sleep bouts. The findings support the hypothesis that blocking KOR receptors can reduce post-dependent drinking, especially in individuals with sleep disturbances, but suggest there may be sex differences in the actions of CYM-53052.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Intramural Research Training Award

Title: Dopamine modulation and in-vivo cAMP signaling activated by dopamine D1 receptor

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Abstract: Dopamine modulation and in-vivo cAMP signaling activated by dopamine D1 receptor Aurora Sheridan[1], Jeong Oen Lee[1], and David M. Lovinger[1*]1 Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism (NIAAA), USA Understanding the intricate signaling pathways (e.g. cAMP) involved in dopamine modulation within the striatum is crucial for elucidating the molecular mechanisms underlying physiological neural adaptation, cognitive functions, and addictive behaviors. Specifically, dopamine D1 receptor is a G protein-coupled receptor (GPCR) linked to Gαs/olf and represents potential therapeutic targets for neurological disorders, including drug addiction and ADHD. While

dopamine D1 receptor-expressing medium spiny neurons (D1-MSNs) play a pivotal role in cellular and behavioral aspects of under drug exposure, the interplay between dopamine release and cAMP modulation in D1-MSN has been difficult to investigate in behaving mice. In this study, we aimed to directly measure changes in cAMP levels and striatal dopamine release while activating D1 receptor-expressing medium spiny neurons (D1-MSNs). To achieve this, we utilized a genetically encoded FRET-based cAMP biosensor in conjunction with a dopamine indicator (GRAB-DA-2m) and pharmacologically modulated D1-MSNs using D1-agonist (SKF-81297). Within our injection protocol, comprising three days of saline injections followed by two days of D1 agonist injections, we observed a significant increase in open-field locomotion in the treatment group receiving D1 receptor agonist (SKF-81297) at doses of 3mg/kg and 10mg/kg compared to the saline injection group. Using in-vivo fiber photometry measurements, we observed elevated baseline levels of dopamine and cAMP in D1-MSNs of dorsolateral striatum (DLS), along with heightened locomotion, following D1 receptor agonist administration. Furthermore, to isolate cell-specific contribution, we tested chemogenetic activation (hM3Dq) specifically in D1-MSNs and found that chemogenetic D1-MSN activation led to an increase in striatal dopamine levels in the dorsolateral striatum (DLS). These findings underscore the significant coupling between D1 receptor activation, cAMP in D1 MSNs, and dopamine release.

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Poster

PSTR131: Alcohol: Neural Circuits and Neurophysiology

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Topic: G.09. Drugs of Abuse and Addiction

Support: Zap Surgical Systems, Inc. San Carlos, CA, USA.
MOST 109-2320-B-002-014-MY3

Title: Modulation of the nucleus accumbens with non-ablative radiosurgery ameliorates alcohol cravings in miniature pigs

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Abstract: Alcohol is the most widely used addictive substance, with approximately 10% of long-term drinkers being diagnosed with Alcohol Use Disorder (AUD) (Carvalho et al., 2019). Since medical and psychosocial treatments have limited long-term effects in controlling alcohol craving, neuromodulation has evolved as a promising new technique in treating severe substance abuse (Coles et al., 2018). The nucleus accumbens (NAc), a small subcortical structure located

deep in the brain, is one of the main neuromodulation targets in concurring alcohol addiction. In this study, we used non-invasive radiosurgery to precisely modulate NAc of miniature pigs with a prolonged drinking history. Our previous findings have shown that low-dose radiosurgery (Dmax=30Gy) can modulate brain metabolic activity without causing structural damage (Yeh et al., 2021). After Lee-Sung miniature pigs (LSPs, n=3) were trained with operant procedures to consume alcohol for more than two years voluntarily, radiosurgery was delivered onto the bilateral NAc of the three LSPs to examine the changes in their voluntary drinking behavior. We obtained structural and functional magnetic resonance images (MRI) right before the radiosurgery and every three months after that for one year. Changes in brain structure were assessed using voxel-based morphometry (VBM) and diffusion tensor imaging (DTI), and alterations in resting-state functional connectivity were tracked using seed-point-based correlation across the entire brain, initially focusing on the relationship between the NAc and the dorsal anterior cingulate cortex (dACC). Our preliminary results showed that LSPs with a long drinking history had smaller NAc volume and lower NAc-dACC connectivity compared to the healthy control LSPs (n=2) with no history of alcohol consumption. Moreover, low-dose radiosurgery could effectively reduce alcohol-craving behavior without changing NAc volume, and the NAc-dACC connectivity was partially restored six months after radiosurgery. These findings contribute to a deeper comprehension of neuromodulation techniques' efficacy and underlying mechanisms in treating AUD, thereby potentially facilitating future clinical research.

Disclosures: C. Lin: None. **K. Chen:** None. **C. Yeh:** None.

Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: BGSU Psychology Department Fund
BGSU Building Strength Grant

Title: Neuroanatomical differences within the mesocorticolimbic circuit in alcohol-preferring rats

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Abstract: The mesocorticolimbic circuit (aka the reward pathway), is a group of neural structures responsible for movement, reward, motivation, craving, reinforcement, and classical conditioning. The striatum is the largest of the structures and includes the caudate nucleus, putamen, and the nucleus accumbens (NAc, core and shell). It is made up of medium spiny neurons (MSNs), which are GABAergic, and typically have two characteristic types: D1 and D2-

type dopamine receptors. The current study is focused on the striatum and NAc and their association with addiction (drug and alcohol). Previous studies have indicated that striatal dopamine signaling and D2 receptors directly impact impulsivity and drug self-administration in both humans and rodents. In humans with alcohol use disorder (AUD), D2 receptors were reduced within the striatum compared to controls correlating to animal research indicating that lower D2 receptor availability plays a role in the vulnerability of developing an addiction. An upregulation of D2 receptors within the core of the NAc has also been found to help reduce alcohol drinking and preferences in both wild-type and alcohol-preferring rodents. Despite the observable behaviors and D2 receptor links to addiction, there has been little research done in comparison striatal volume and cell counts between P rats and controls (Wistars). The current project aims to compare the neuroanatomy of the striatum and the NAc (core and shell) between P rats and Wistars (who have both had previous alcohol exposure) using immunohistochemistry (IHC) for tyrosine hydroxylase (TH), Nissl and microscopic techniques. We examined dopaminergic fiber density, estimated total area volume, total cell counts (Nissl), and have a small pilot data of estimated total D2 receptors. Preliminary results suggest that P rats have no significant difference between the striatum and shell volume compared to Wistars, however, they do have an increased IHC TH volume within the core of the NAc. Increased core volume could indicate a deficit to cognitive processing for reward and reinforcement which could lead to more explanations and insights to understanding addiction.

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Poster

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Title: Tip60 plays a critical role in alcohol-induced transcriptional neuroadaptations

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Abstract: Alcohol consumption causes a homeostatic imbalance in the organism, followed by the development of neuronal adaptations, such as alcohol tolerance and physiological dependence. Histone acetyltransferases (HATs) have emerged as candidate regulators of gene expression involved in alcohol-induced neuroadaptations. This study aims to evaluate the role of Tip60 HAT in these adaptations and identify master regulators of genes associated with Tip60 activity. For our approach, we used the model organism Drosophila melanogaster and the advantages of the Gal4/UAS System and RNAi to generate a line of transgenic flies with Tip60 knockdown (Tip60 KD) in neurons. We functionally tested Tip60 KD flies to be exposed to an acute dose of ethanol at different time points to investigate the temporal dynamics of ethanol tolerance. Then, we will perform an RNA-sequencing for transcriptional analysis of the flies' brain. Our results showed that tolerance was significantly decreased on Days 1, 2, and 7 after an initial exposure to ethanol. RNA sequencing of Tip60 KD flies revealed reduced expression of myofibril assembly and protein phosphorylation genes, and increased expression of defense response and immunological genes. Therefore, immune responses may be a fundamental response of the brain to ethanol regulated by Tip60. Furthermore, results from motif enrichment analysis highlight the transcription factors Dif (normalized enrichment score = 7.42), dl (NES = 4.97), and Rel (NES = 3.41) as key master regulators of the Tip60 KD upregulated genes. Conversely, for the downregulated genes, we identified the transcription factors Poxn (NES = 5.39) and prd (NES = 5.24). This study showed that Tip60 may be a candidate regulator of alcohol-induced gene expression through the activation of key transcription factors.

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Poster

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5R25GM061151-22
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Title: Epigenetic mechanisms of alcohol neuroadaptations in Drosophila ventrolateral neurons (LNv)

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Abstract: Uncontrolled alcohol consumption affects neurological, physiological, and behavioral processes that can affect young people and adults. Alcohol consumption causes a homeostatic imbalance in the body, followed by the development of adaptations in the brain that lead to alcohol tolerance and physiological dependence. These adaptations can also affect the mechanisms of neural homeostasis and sleep, presenting a major problem in recovery from alcoholism. Recent studies provide evidence that modulation of gene expression is an important mechanism in the development of brain adaptations that produce alcohol-induced behavioral changes. However, many of the epigenetic mechanisms controlling transcriptional reprogramming in alcohol-induced neuroadaptations remain unexplored. In this study, we aim to determine the role of the histone acetyltransferase Tip60 during alcohol-induced disorders using a *Drosophila* model. This study focuses on the ventrolateral neurons (LNv), a small group of neurons known to regulate sleep/wake cycles in *Drosophila*. Because of its role in the acetylation of histones, we hypothesize that Tip60 activity in LNv mediates alcohol-associated transcriptional adaptations that result in alcohol tolerance and sleep dysregulation. To test this hypothesis, we use the UAS-GAL4 system to manipulate Tip60 expression within LNv and analyze alcohol-induced behavioral alterations. Our results show a significant reduction in tolerance development after the knockdown of Tip60 with RNA interference (RNAi) in LNv. In addition, we recently evaluated the effects of alcohol exposure on the morphology and physiology of LNvs. Preliminary experiments show that alcohol exposure changes neuronal morphology and production of pigment dispersion factor (PDF) neuropeptide by the LNvs. Moreover, we show that these changes are dependent on Tip60 expression. Together, our results suggest that Tip60 is a key epigenetic modulator of alcohol responses in LNv neurons. Understanding the molecular, physiological, and cellular mechanisms underlying ethanol neuroadaptations potentially leads to the identification of new therapeutic targets for alcohol-induced disorders.

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

Title: Intraccumbal administration of CB2 agonist GW405833 reduces the expression of methamphetamine-induced locomotor sensitization

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Abstract: INTRODUCTION: Locomotor sensitization (LS) is the progressive and persistent enhancement of a behavioral response to psychostimulant drugs such as cocaine, amphetamine and methamphetamine (METH) after repeated and intermittent administration. LS has been associated with its ability to increase dopamine (DA) levels in nucleus accumbens (nAcc) and some drug addiction-related features in humans. It has been suggested that activation of cannabinoid type 2 (CB2) receptors attenuates psychostimulant-related behaviors because these receptors are expressed on VTA DAergic terminals in nAcc. CB2 receptor activation inhibit DA release in nAcc and regulates psychostimulant-related behaviors. In the present study, we evaluated the effects of intra-accumbal administration of CB2 agonist GW405833 on the expression of METH-induced LS. METHOD. Male Wistar rats were divided in four groups (n=6) and treated with METH or saline during days 3-7 (development of METH-induced LS). On day 10 (expression of METH sensitization test) rats were treated with drugs. Group S-S was treated with saline, group M-M was treated with METH, group M-GWM(0.5) was treated with GW405833 (0.5 µg) and METH, group M-GWM(0.25) was treated with GW405833 (0.25 µg), and METH. METH was administered ip and GW405833 was administered into nAcc shell (AP 1 mm from bregma, ML ± 1.3 mm, DV -6.8 mm). The behavioral activity was recorded for 60 min on open-field cages during development and expression of METH-induced LS. The names of the groups refer to the treatment received during the development and expression test of METH-induced locomotor sensitization. RESULTS. The data showed that administration of METH induced an increase in locomotor activity in rats during the development and expression phase. However, GW405833 administration in the expression phase produced a reduction of the effect on METH-induced LS. CONCLUSION: These results are in line with previous studies and suggest that CB2 agonist GW405833 could be acting on DAergic nerve endings and plays an inhibitory role in the regulation of DA release into the nAcc, essential for the development and expression of psychostimulant-induced LS. <!--EndFragment-->

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: TRR 265

Title: Neural Correlates of Social Drinking Facilitators in Mild to Moderate AUD: A Multimodal Neuroimaging and Real-Life Study

Authors: *A. GHADAMI[1,2], E. BILEK[2], A. SREEPADA[2], J. ANDOH[2], M. REICHERT[3], R. SPANAGEL[4], A. S. MEYER-LINDENBERG[5], C. M. HEIM[6], H. TOST[2];
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Abstract: This study aims to uncover the relationship between the social environment and its effects on individuals with mild to moderate Alcohol Use Disorder (AUD). Participants' AUD was verified by DSM-V criteria, and the severity was quantified using the Alcohol Use Disorders Identification Test (AUDIT) (mean = 14.89 SD = 5.20). By investigating the neural basis of social drinking, we aim to identify factors that predispose individuals to alcohol consumption in social settings. This project bridges the gap between social drinking behaviors and the underlying neural activities, enhancing understanding of the interplay between environmental influences and neural responses in AUD. Utilizing Ecological Momentary Assessment (EMA) in a generalized mixed-level analysis, we investigated the effects of surrounding drinkers and current drinking status to derive a Social Drinking Risk (SDR) index. Voxel-Based Morphometry (VBM) and structural covariance analysis assessed the impact of SDR on brain structure, complemented by functional MRI data examining brain activity responses using an alcohol cueing task. Significant findings revealed that social environments substantially influence drinking behaviors in AUD individuals (beta-coefficient = 1.4419, SE = 0.08114, p-value < 0.0001, n = 83). Furthermore, we observed distinct neural patterns in participants with varying levels of SDR. Specifically, those with higher SDR demonstrated a reduced gray matter volume in the pregenual anterior cingulate cortex (pgACC) (T= 5.17 p-value < 0.001) and altered structural covariance between the pgACC and ventral striatum (vStr) (T = 2.99 p-value = 0.047), suggesting a neural predisposition for increased drinking in social settings. Additionally, participants with lower SDR showed increased brain activity in these regions when reorienting attention away from alcohol-related cues (pgACC: T = 3.55, p = 0.037; vStr: T = 3.37, p = 0.023), indicating a more pronounced neural response in individuals less influenced by social drinking cues, suggesting a potential protective social neural phenotype. This study provides evidence that social contexts significantly influence drinking behaviors and are associated with distinct changes in brain structure and function. The observed brain patterns in individuals with higher SDR might contribute to their susceptibility to social drinking cues, while those with lower SDR may possess higher neural capacity to reorient their attention away from social alcoholic cues. These findings underscore the value of multimodal neuroimaging techniques in enhancing our understanding of AUD, offering potential pathways for targeted interventions.

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Poster

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Topic: G.09. Drugs of Abuse and Addiction

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Title: Neural correlates of stress and alcohol cue response in individuals with pain and alcohol use disorder

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Abstract: Alcohol misuse and pain are often comorbid, and have been linked to adverse mental and physical health outcomes. Despite their frequent co-occurrence, the neurobiology underlying the association between alcohol misuse and pain is not well-understood. Stress neurocircuits overlap with pain and alcohol reactivity and previous work has shown dysregulated stress and reward circuits linked to alcohol craving, but how those with pain symptoms respond is not known. Here, social drinkers (SD) and individuals seeking treatment for alcohol use disorder (AUD) completed the Cornell Medical Index to evaluate pain symptoms. Participants were classified as presenting either with pain symptoms (Pain+: 17 AUD; 14 SD) or without pain symptoms (Pain-: 23 AUD; 14 SD). All subjects completed a well-validated fMRI paradigm involving stress, alcohol, and neutral cue exposure with repeated self-reported assessments of alcohol craving. Using whole-brain, voxel-based second level 3dLME (AFNI) analyses (p<.001, whole brain cluster correction at α<.05), we found that Pain+ versus Pain- evidenced greater dorsal anterior cingulate cortex and left amygdala hyperactivation during the neutral condition, but hypoactivation during stress-neutral contrast. In addition, Pain+ exhibited blunted right anterior insula (AIC) during stress relative to neutral cue exposure, as well as blunted anteromedial thalamus and left AIC and hyperactive orbitofrontal cortex (OFC) during alcohol relative to neutral cue exposure. Relative to SD with pain, we further observed that AUD patients with pain exhibited hyperactivity bilaterally in AIC and hypoactivity in right dorsal caudate during alcohol relative to neutral cue exposure. Most notably, alcohol-cue induced craving, which was significantly higher in Pain+ (p=.03), correlated significantly with blunted right AIC and OFC responses during alcohol relative to neutral cue exposure. These results provide first evidence of disrupted cortico-striatal-limbic reactivity to alcohol and stress cues and heightened alcohol cue-elicited craving in the pain+ vs pain -groups with differential neural responses in those with and without comorbid AUD. These findings support to the need to further study stress and drug cue reactivity in those with comorbid pain and AUD to facilitate the development of targeted prevention and treatment efforts for comorbid pain and AUD.

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Poster

PSTR132: Prefrontal Cortex in Non-Human Primates

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Title: Behavioral and neural correlates of complex thoughts

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Abstract: Careful consideration of complex problems is a time intensive process that ultimately informs decisions. Despite the central role of complex thought in the human experience, we lack systems- and circuit-level answers to fundamental questions such as: how do we think? and why are some thoughts more difficult than others? We created a nonhuman primate (NHP) task that incentivized NHPs to find optimal or satisfactory solutions to computationally demanding problems. NHPs invest time to construct and compare multiple combinations and the time invested reflects the number of computational steps efficient algorithms require to achieve good outcomes (Hong and Stauffer, 2023, NatNeuro). In head fixed animals, we analyzed eye movements while animals considered these difficult problems. When the animals' behavioral solutions suggested that the animals considered items one-at-a-time, the eye movements were governed by the single-item values - the animals spent more time dwelling on high value items rather than low value ones. On the other hand, when the animals' solutions resembled those produced by combinatorial search, the eye movements were not correlated with single-item values, but rather with the 'combinatorial importance' - defined as the number of occurrences of an item in good or optimal combinations. Thus, the search trajectories provided further support that the animals used distinct thought processes to generate different behavioral strategies. To investigate the neural correlates of these thought processes, we record single unit activities in the dorsolateral prefrontal cortex (dlPFC) during the task. Neurons in dlPFC encode key variables that characterize the mental operations the animal performs. A significant proportion of neurons modulate their firing rates according to the complexity of the behavioral strategies (n = 14/41). Moreover, two distinct subpopulations show differential ramping responses based on the length of the deliberation time (n = 5/41) and the size of the search space (n = 3/41), defined by the unique number of items scanned. In addition to searching for good combinations, the animals also need to keep track of the accumulated rewards to achieve satisfactory outcomes. Time-locked to item selections, neurons' phasic activities correlate with the value of the selected item before and the accumulated rewards after each selection ((n = 7/41 and n = 10/41 respectively). Overall, these data begin to reveal how dlPFC contributes to complex thinking in primates.

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Poster

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Title: Using a layer 3 pyramidal neuron specific enhancer for optogenetics in NHP dlPFC

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Abstract: Cell type specific neural circuits are the foundation of adaptive behaviors and cognition, but the application of cell type-specific manipulations in nonhuman primates (NHPs) remains limited. One promising approach is to use distal regulatory elements, known as enhancers, to drive cell type-specific adeno-associated viruses (AAVs) expression. We previously performed multiomic analysis of NHP dorsolateral prefrontal cortex (dlPFC) and isolated an enhancer for layer three pyramidal neurons (L3PNs). We used this enhancer to drive expression of GFP and demonstrated that the vast majority of GFP expression was restricted to L3PNs. Here we set out to optimize the protocol for using this virus with one popular circuit-breaking tool: channelrhodopsin (ChR2). We cloned the enhancer, the ChR2 gene, and a unique DNA barcode into AAV plasmid backbones. We packaged the constructs into three different NHP neurotropic AAV variants AAV9, AAV.X1.1, and AAV.PhP.eB. We used an MRI-guided robot to place injections of the enhancer driven AAV variants along the principal sulcus of a cynomolgus macaque monkey. Two months after AAV injection, we euthanized the animal via transcardial perfusion. The brain was cryoprotected and cut in the coronal plane. We characterized and quantified the regional expression of the pyramidal neurons from each serotype using histological analysis and comparing distribution of fluorophore-expressing neurons across cortex. Current data suggests a difference in spread between AAV.X1.1 and AAV9. Specifically showing that AAV.X1.1 infects more layer three pyramidal cells within a section and covers more area in the anterior-posterior range. We injected a second monkey with AAVX1.1-L3PNenh-ChR2, and future studies will explore the ideal parameters for stimulation. Together, these results provide a blueprint for causal manipulation of the highly recurrent neurons in layer 3 of the dorsolateral prefrontal cortex.

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Poster

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Title: Optimistic and pessimistic beliefs define choice values under ambiguity

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Abstract: Nearly every decision includes some level of uncertainty, and managing that uncertainty is a critical component of adaptive decision making. Two forms of uncertainty are formally recognized: risk, when potential outcomes and their probabilities are known, and **ambiguity**, where the probabilities are not known. We and others have described the neural encoding of probability distributions under risk, but the mechanisms driving ambiguity attitudes remain poorly understood. Ambiguity attitudes require fundamentally distinct computations compared to risk. Whereas risky uncertainty can be directly calculated, from experience or instruction, ambiguous uncertainty cannot be calculated. Instead, decision makers must rely on subjective probability judgments, i.e. beliefs. Here, we present a novel task for the estimation of those beliefs under ambiguity: the method of distributional equivalents. In this task, risky gambles were presented via informative visual bar cues: these informative visual cues independently indicated the potential magnitudes and their associated probabilities using a two-dimensional scale, and ambiguity was introduced by masking the probability dimension. Bar gambles of identical magnitudes but varying probabilities allowed us to determine the distributional equivalents for ambiguous options. We find that distributional equivalents diverge significantly across all reward magnitude ranges tested. Specifically, NHPs make *pessimistic* estimates of underlying probability distributions when the value of reward outcomes is large, whereas small reward outcomes result in *optimistic* estimates of underlying probability distributions. In other words, NHPs hold systematically inconsistent beliefs about ambiguous probabilities based on the reward magnitudes on offer. These inconsistent beliefs drive diverse ambiguity attitudes. We are currently recording from dlPFC in order to uncover the neurophysiological correlates of decision making under ambiguity. Ultimately, our work will reveal the biological and computational underpinnings of irrationality and subjective beliefs.

Disclosures: W. Kerkhoff: None. **W.R. Stauffer:** None.

Poster

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Title: A semi-automated MRI-based pipeline for in-vivo assessment of excitotoxic lesions in macaque brains

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Abstract: Neuropsychological studies that make use of permanent lesions are a crucial tool to study brain function (Vaidya et al., *TICS*, 2019). Excitotoxic lesions made with ibotenate (IBO) or similar agents have proven especially valuable; excitotoxins produce neuronal cell loss in a circumscribed region while sparing white matter tracts. Traditional histological evaluation of a brain lesion can only be done *post mortem*, delaying confirmation of the lesion site and interpretation of the behavioral data. This issue can be addressed by estimating the lesion extent with *in vivo* MRI acquired within days of the IBO injection. The localized transient edema caused by the injection and/or by inflammation and cell death appears as hypersignal in T2-weighted MRI and, in many brain regions studied so far, the location and extent of the hypersignal corresponds closely with the location and extent of neuronal loss (Malkova et al., *Hippocampus*, 2001; Basile et al., *Front Integr Neurosci*, 2017). Typically, the extent of the hypersignal is assessed visually on individual MRI slices. This method of assessment is both labor intensive and potentially prone to significant thresholding variability across slices, cases, and raters. Here we present a semi-automated procedure for IBO lesion estimation from T2 MRI in macaques. The threshold still needs to be set by a human, but the risk of bias is greatly reduced by deriving the threshold from the difference between overall voxel intensity distributions after vs. before the injection, without explicit reference to the injection site. Other decisions that are not automated (cropping and disregarding spurious clusters) have a low risk of bias. The processing pipeline is implemented in AFNI and MATLAB. The input data are T1- and T2-weighted MRI volumes acquired before the surgery and several days after the surgery. 3D estimates of lesion volumes are the primary output. Because the pipeline operates in a common template (NIMH Macaque Template, NMT) space, lesion comparisons across multiple animals and atlas-based quantifications of percent damage to defined brain areas can be easily made. Although high quality preoperative and postoperative T1 and T2 whole-brain scans provide the best result, the pipeline can produce usable results from lower quality scans, partial-brain scans, or when some of the scans are missing. The ultimate verification of the pipeline awaits histological verification of lesions in our macaques. Until that time, however, the present method offers a major advantage: the ability to obtain unbiased estimates of lesion extent soon after injection of excitotoxins.

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Poster

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Title: Exploring the role of macaque anterior cingulate cortex and autonomic modulation in reward expectancy

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Abstract: Dysfunction of the anterior cingulate cortex (ACC) has been implicated in neuropsychiatric disorders such as schizophrenia, attention deficit hyperactivity disorder, and obsessive-compulsive disorder (Reid et al, *Biol Psychiatry*, 2010; Bush et al, *Biol Psychiatry*, 1999; Fitzgerald et al, *Biol Psychiatry,* 2005). Evidence from studies in macaques suggests that the ACC contributes to social cognition, decision making, and reward expectancy (Chudasama et al, *Cereb Cortex*, 2013; Basile et al, *PLoS Biol*, 2020; Shidhara & Richmond, *Science*, 2002). Additionally, the ACC is involved in the regulation of autonomic states (Seamans and Floresco, *Neurosci Biobehav Rev*, 2022). Preliminary findings from our laboratory suggest that the ACC is essential for the expression of autonomic correlates of reward expectancy (Kusmierek et al, 2023 Neuroscience Meeting Planner, Program # PSTR433.19). Whereas control monkeys showed an increase in heart rate (HR) in anticipation of expected rewards, monkeys with bilateral neurotoxic lesions of the ACC did not. To better characterize the role of the ACC in this task setting, we investigated whether the change in HR was specific to anticipation of reward or due to a more general disruption of the HR control by behavioral events. To accomplish this, we added additional subjects to the study, altered the conditions of reward delivery, and monitored HR around the period of reward delivery (trial outcome) as well as during reward anticipation. In the original task, monkeys viewed a pair of slowly moving visual stimuli that predicted reward delivery 100% of the time. The modified task included a small number of catch trials (12.5%) in which no reward was delivered despite otherwise identical stimulus conditions. The addition of catch trials allowed us to examine changes in HR in the context of reward omission. A total of 11 rhesus macaques *(Macaca mulatta)* were studied: six received bilateral neurotoxic ACC lesions and five served as unoperated controls. In the subset of animals tested with catch trials (N = 2 ACC lesion; N = 5 control), monkeys with ACC lesions displayed a significant difference in HR during the time after trial outcome on trials with reward delivery versus reward omission, as did four of the five controls. These data suggest that the contribution of the ACC to HR increases in anticipation of reward in our original experimental setting is specific to expectation and not to a more general disruption of the control of HR by behavioral events. In future studies, we aim to explore the role of the ACC in mediating autonomic regulation in additional behavioral contexts using additional autonomic measures.

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Poster

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Title: Learning decouples accuracy and reaction time for rapid decisions in dorsolateral prefrontal cortex

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Abstract: We trained macaque monkeys (N=2) on a serial learning transfer task in which they learned the implied order in a list of 7 novel pictures in each session, indicating their choices with saccadic eye movements. They reliably learned each new list order within 200-300 trials with asymptotic accuracy of around 80-90% correct. Choice saccade reaction times median averaged 217 and 274 msec for the two NHP, respectively, compared to simple RTs of 181 and 182 msec. There was a Symbolic Distance Effect (SDE) such that accuracy for adjacent list items was 60% and increased to 90% for the largest symbolic distance. Although performance accuracy improved with learning and symbolic distance, reaction times were constant. Behavioral data were fit with a six-parameter Generalized Drift-Diffusion Model (GDDM). We recorded 275 dorsolateral prefrontal (77 frontal eye field, 198 periarcuate) neurons. The population of neurons was robustly modulated by saccade target selection, learning, and symbolic distance. However, the dynamics of the neuronal responses did not match those predicted by the GDDM. Thus, while dlPFC neurons were modulated by learning-related signals prior to rapid choices, their responses did not appear to directly represent stochastic evidence accumulation.

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Poster

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Title: Neural population geometry during flexible deductive reasoning

Authors: *S. VYAS[1], T. FAKHOURY[2], E. TRAUTMANN[3], A. LITWIN-KUMAR[4], M. N. SHADLEN[5], M. M. CHURCHLAND[4];
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Abstract: Cognitive flexibility suggests that subjects can solve the same problem using different strategies. To investigate, we designed a novel deductive reasoning task where monkeys used abstract rules to plan a multi-reach sequence and hold it in working memory until a go-cue. A size rule required targets be touched in order of increasing size. A color rule required alternation between red and blue targets. Each trial presented a previously unseen arrangement of targets and cues, requiring a novel solution. During a delay period, monkeys had to apply the correct rule based on the stimulus to decide the order in which the targets should be touched. The necessary cognitive processing is context (rule) dependent, yet the task can create situations where the solution (and thus motor output) is matched across contexts. We recorded over 500 neurons simultaneously using Neuropixels-NHP probes within motor cortex (M1), supplementary motor area (SMA), and lateral prefrontal cortex (LPFC: 8, 9/46, and 47). We hypothesized that a brain region that solves the task must 1) be context-sensitive, i.e., distinguish two trials where the rule is different, but the motor output is matched, and 2) reflect the target locations of all elements within the sequence during the delay period. We found that M1 delay period activity is insensitive to both the rule and the full sequence; it reflects only the first reach, and information regarding each subsequent reach arrives ‘just in time’ as the previous reach ends. In SMA, we could decode the identity of all reaches during the delay period but found no rule information. Thus, SMA is critical for sequence generation but does not participate in sequence determination. LPFC delay period activity reflected both the rule and the full sequence. Our population analysis revealed that each distinct reach location becomes specified ~150ms after one another in independent ‘ordinal rank’ subspaces. Via this mechanism, decision computations to select each target occur sequentially, despite all stimuli being present at once. Our analyses found that the monkey predominantly used backwards induction: solving the task by first deciding the final target in the sequence, then the second, then the first. On single trials, we also found other ordering strategies, which are influenced by recent errors and target arrangement. We propose a computational mechanism whereby an attentional system extracts task-relevant features from the stimulus for each target. This information arrives sequentially in LPFC, where the dynamics map the inputs into an appropriate ordinal rank subspace. Dynamic use of these subspaces drives flexibility in decision timing and strategy.

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Poster

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Topic: H.03. Decision Making

Title: Dynamic evolution of the decisional reference point across frontal brain regions in the monkey

Authors: *P. GLIMCHER[1], D. NGUYEN[2], E. L. RICH[3], J. D. WALLIS[4], K. LOUIE[5]; [1]Neurosci. and Physiol., New York Univ. Grossman Sch. of Med., New York, NY; [2]New York Univ. Grossman Sch. of Med., New York, NY; [3]Neurosci., Mount Sinai Sch. of Med., New York, NY; [4]U.C. Berkeley, Berkeley, CA; [5]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The reference point (RP) is a hidden benchmark against which a decision maker evaluates options and is central to theories of decision making. However, little is known about where the RP is represented in the brain and how it shapes the neural computations guiding the decision process. Here we reanalyzed a dataset from a previously published paper (Rich & Wallis, 2014) with two key features: (1) a stimulus-response task where earned within-trial reward value was fixed but cumulative across-trial reward (the RP) varied; and (2) neural recordings from multiple frontal brain areas involved in value-guided decision-making. These features allowed us to investigate the neural representation of reference point and reference-dependent values. Two NHP subjects were trained to perform a task in which rewards were delivered after every 6 trials. Each trial began with a reward bar indicating the current cumulative reward amount. After fixation, subjects were presented with a visual cue instructing a left or right response. Four cues were used, differing by correct response (left/ right) and valence (positive/ negative) in a 2×2 design. Positive cues resulted in one unit increase or no change in reward for correct and incorrect responses, respectively; negative cues resulted in no change or one unit decrement in reward. Subjects received feedback through a change (or no change) in the reward bar size. After every sixth trial, subjects received a juice reward the magnitude of which was proportional to the size of current reward bar. In this task, the reward bar functions as the RP against which individual trial outcomes may be evaluated. We examined the independent effects of reward and RP information on activity of 977 neurons recorded from six different frontal cortical regions (dACC, vACC, dlPFC, vlPFC, OFC, mOFC). Regression analyses showed a dynamic and distributed representation of RP-related neural signals, with the involvement of different frontal brain regions at different points in the decision process. Early in the trial, a homogenous population encoding of the RP was the strongest in the vACC. During cue onset, reference-driven modulation shifted to the dACC, which showed a reference-dependent coding of cue valence. Finally, at the end of the trial, RP information modulated outcome coding in the dlPFC. Our results reveal a distributed representation across frontal brain areas that correlates with the reference point and reference-dependent values. The evolution of these computations throughout the decision process is mirrored by an anatomical transition from ventral to dorsal areas, providing a neurobiological substrate for the influence of the RP on decision-making.

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Poster

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Title: Hierarchical organization in the frontal lobe during perceptual decision-making

Authors: *T. WANG[1], N. CARR[1], K. LEE[2], P. O. BOUCHER[3], V. MOOSMANN[4], C. CHANDRASEKARAN[5];
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Abstract: The frontal lobe is fundamentally important for cognition and motor control. fMRI studies in humans and tracer experiments in monkeys suggest a hierarchical organization with a rostro-caudal and dorsal-ventral functional gradient within the frontal lobe. However, how these functional gradients are involved in perceptual decision making is not well understood.
We used V-probes and Neuropixels to record from the dorsolateral prefrontal cortex (DLPFC), periarcuate cortex, and dorsal premotor cortex (PMd) in macaque monkeys performing two variants of our red-green checkerboard discrimination task. In the targets-first task (TF), two targets (red and green), were shown to the monkey with two target configurations (Red left and Green right, or vice versa) to unmix signals related to color choice from action choice. After a target viewing period, a checkerboard composed of red and green squares appeared. Monkeys discriminated the dominant color in the checkerboard and reached to and touched the target corresponding to the dominant color. In the checkerboard first task (CF), we switched the order of the checkerboard and targets while remaining the same task rule.

While monkeys performed this task, we recorded neural activity over a wide range of spatial locations in the DLPFC (182 sessions from DLPFC, T: 127 sessions; V: 36 sessions; Z: 19 sessions) and PMd (146 sessions from PMd, T: 80 sessions; O: 66 sessions). We localized DLPFC Brodmann areas (including 9/46d, 9/46v and 8Ad) through MRI and LFP power spectrolaminar analysis (Mendoza-Halliday et al, 2024). We observed that high-level task signals including target configuration and color choice/color evidence was most prominent in ventral and rostral aspects of DLPFC and less apparent in dorsal and caudal aspects of DLPFC. In contrast, action choice signals (left vs right) increased from DLPFC to PMd. Preliminary simultaneous recordings between 9/46 and PMd suggested that choice signals in 9/46 emerge earlier than in PMd. Finally, most PMd units showed a generalized action choice signal across tasks while DLPFC, especially, 9/46v showed a task specific modulation as a significant number of units demonstrate task-dependent variability in modulation.
Collectively the results suggest a hierarchical organization of the frontal lobe in-vivo for perceptual decisions, and imply that DLPFC computes action choice, and is a likely source of choice signals in PMd. Ongoing work aims to test this hypothesis using causal approaches paired with simultaneous recordings.

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Poster

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Title: Neurons in the monkey prefrontal-striatal network encode cognitive state and reward prediction error in a bandit learning task

Authors: *S. M. BRUNSON[1], C. S. CHEN[2], B. A. EBITZ[4], K. J. BONE[1], M. V. CHAFEE[3]; [1]Neurosci., [2]Psychiatry and Behavioral Sci., [3]Neuroscience/Brain Sci., Univ. of Minnesota, Minneapolis, MN; [4]Neurosciences, Univ. de Montréal, Montréal, QC, Canada

Abstract: Schizophrenia impairs cognitive functions including decision making. To characterize the neural mechanisms potentially disrupted in the disease, we translated a 3-arm restless bandit decision making task to nonhuman primates and recorded neural activity in the prefrontal cortex (PFC) and striatum (STR) during task performance. People with schizophrenia exhibit altered choice dynamics in the task, less frequently selecting the choice with the highest reward probability, suggesting impairment in the processes of updating the values of available options over trials. In the 3-arm restless bandit task we trained monkeys to perform, an array of 3 choice stimuli was presented each trial at randomized locations. Monkeys selected a choice stimulus by

moving a joystick to the stimulus, receiving a probabilistic reward based on the stimulus identity (rather than location). The reward probabilities associated with the three choice stimuli walked randomly and independently over trials. We fit hidden Markov models to sequences of choices to identify periods of exploration (sampling all 3 choice stimuli) and exploitation (predominantly choosing the choice stimulus with the highest reward probability), finding that monkeys alternated systematically between these phases as reward probabilities changed. This indicates that they integrated action and reward outcomes over trials to update the reward values associated with each choice stimulus, and maintained the high-reward choice as a cognitive state representation to guide choice selection over trials.
We found populations of neurons in both the PFC and STR that encoded the identity of the selected choice stimulus for each trial, both after and before the choice stimulus array was displayed. These neural signals reflect a predictive cognitive state variable encoding the high reward probability choice that was learned through trial-and-error and that persisted over trials, potentially guiding behavior during the exploit phase. Notably, we found significantly fewer neurons encoding choice stimulus identity at all time points in a pharmacological model of schizophrenia where an NMDAR antagonist is administered. In addition, we found neurons within the PFC that encoded both the sign and magnitude of the trial-by-trial reward prediction error (as quantified by a Bayesian learning model fit to choice data), suggesting that prefrontal neurons encode error signals that could be used to update the value of cognitive states. These results characterize the neural mechanisms of state encoding and updating in the prefrontal-striatal circuit, the disruption of which may underlie decision making deficits in schizophrenia.

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Title: Neural mechanisms of response inhibition and self control in non-human primates

Authors: *J. ELSEY[1], V. STUPHORN[2];
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Abstract: In everyday life, we must often interrupt or suppress a behavior in favor of others that are more appropriate in the current circumstances or in accordance with our long-term goals. Behavioral control is a fundamental component of executive control that is responsible for the suppression of actions, thoughts, and emotions. Two key aspects of behavioral control are

response inhibition and self-control. Response inhibition is the ability to deliberately stop a prepared motor response. Self-control is the ability to inhibit self-defeating behavior in the face of temptation. Human imaging and lesion studies have identified several prefrontal regions that are active during tasks requiring these two forms of behavioral control, however it is unknown whether the neural mechanisms that determine the success or failure of response inhibition or self-control are shared or distinct. To address this, we recorded single-unit neurons using linear vector arrays (129 penetrations) from the Frontal Eye Field (FEF: n = 269), Supplementary Eye Field (SEF: n = 286), Dorsolateral Prefrontal Cortex (DLPFC: n = 313), and Ventrolateral Prefrontal Cortex (VLPFC: n = 169). We trained macaque monkeys to switch between saccade stop-signal (countermanding) and self-control tasks completed in 20 trial blocks. In the countermanding task, the monkey made a saccade to a peripheral target. On a subset of trials, a visual stop signal was presented after a variable stop-signal delay. In the self-control task, the monkey made a saccade to indicate their choice between a smaller, sooner (S) and a larger, later (L) reward. On a subset of trials, termed temptation trials, the unchosen option remained available at which point self-control must be exerted to the resist the suboptimal S option in favor of the L option. Temptation trials provide a clear behavioral marker for the level of self-control exerted on a trial-by-trial basis. The monkeys reliably switched between stop-signal and self-control tasks. Failures of self-control that led to increases in L-S switching on temptation trials and resulted in a leftwards shift of the choice function. Critically, in this situation of heightened need for self-control, the monkey was sometimes able to resist temptation and sometimes failed to do so. Data analysis is ongoing, but we find proactive control (early selection of goal-relevant information) and reactive control (late-recruited correction mechanism mobilized after the detection of a high interference event) signals throughout PFC, suggesting that motor and motivational control may share a common neural circuit.

Disclosures: J. Elsey: None. **V. Stuphorn:** None.

Poster

PSTR132: Prefrontal Cortex in Non-Human Primates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.12/J27

Topic: H.03. Decision Making

Support: DAPA Grant 915027201
MOTIE Grant 1415181023

Title: Adaptive Decision-Making in Economic Choices: Neural Dynamics and Timing Influences in a 2AFC Paradigm

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Abstract: Understanding the timing of decisions enhances our comprehension of the cognitive mechanisms driving economic choices. Unlike perceptual decision-making, which benefits from the controlled manipulation of stimuli, economic decision-making involves complexities such as risk, preferences, experiences, and cognitive biases, making it difficult to accurately pinpoint the exact moment of decision. To tackle this issue, we adopted a reinforcement learning framework to estimate the value of options in a two-alternative forced choice (2AFC) paradigm. Later on, we employed the sequential sampling model framework to determine decision times. We trained a male rhesus monkey to perform a 2AFC task using a joystick, presenting seven blocks with different probabilistic rewards for each option. The trials included a variable delay epoch ranging from 300 to 1000 ms between target presentation (TP) and the Go Cue (GC). We evaluated how the GC's timing affects decision time by comparing two inverse Gaussian distributions—one centered at GC and another at the model-estimated decision time. We categorized trials as 'affected' or 'unaffected' based on whether the timing of the Go Cue (GC) influenced the decision time. Notably, as the delay increased, the likelihood of it affects the decision time rose, particularly for delays starting at 746ms. In affected trials, shorter delays tended to accelerate decision times, whereas longer ones delayed them. Neural recordings from the DLPFC via a Utah array showed a gradual decrease in firing rates leading up to the GC in unaffected trials, whereas accelerated ‘affected’ trials exhibited a sharp drop in firing rates around 700 ms prior to the GC, followed by a recovery phase 300 ms before the GC, aligning with the firing rates of delayed ‘affected’ trials. Fluctuations in DLPFC activity suggest that the brain adapts its cognitive processing during decision-making. Specifically, in trials affected by timing delays, neural dynamics indicate a compensatory response to maintain decision consistency despite variable intervals. This demonstrates the brain's resilience in adapting to temporal uncertainties, preserving decision accuracy across different conditions.

Disclosures: S. Kim: None. **M. Kim:** None. **H. Park:** None. **J. Sohn:** None.

Poster

PSTR132: Prefrontal Cortex in Non-Human Primates

Location: MCP Hall A

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Program #/Poster #: PSTR132.13/J28

Topic: H.03. Decision Making

Title: Multiplexing of value signals in the primate frontostriatal network during a strategy board game

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Abstract: During competitive board games, such as tic-tac-toe or go, players need to update the values of alternative moves dynamically depending on the previous and anticipated moves of their opponents. In order to investigate how the values of self and opponent’s actions are

computed and represented in the brain, we trained two rhesus monkeys to play a competitive strategy board game called a four-in-a-row. During this game, the monkeys placed their stones one at a time using a joystick on a 4-by-9 board while taking turns with a computer opponent. Each player could win by placing 4 stones in a row horizontally, vertically, or diagonally, and the animal was rewarded only for wins. We developed a model of behavior that used a logistic regression over heuristic game features to predict the monkey's next move. The model demonstrated a sensible ordering of heuristic features, suggesting that the monkeys develops differentiated values of task-relevant heuristics. Neural activity was recorded from the dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), and caudate nucleus (CD) of one monkey using two 64-channel silicone probes simultaneously in two of these areas in a given session. During the recording experiment, the computer opponent always initiated the game, and probabilistically alternated between defensive and offensive strategies while making its move randomly with a small probability so that the probability of winning for the animal did not become too low. We used a linear regression to account for neural signals using the value of the move, the number of stones on the board, and whether the animal wins the game. We used the maximum number of stones connected by the current move of each player (connection length) to estimate the value of the chosen position. We found that many neurons in all regions tested in this study modulated their activity according to the values of the animal's own moves as well as those of the opponent. To examine how these different value signals are spatially and temporally multiplexed within each brain area, we examined the correlation coefficient matrix of the regression coefficients related to the self and opponent connection lengths. We found that the difference between these two value signals was reflected in the activity of dmPFC, while they influenced the activity of dlPFC and CD neurons similarly with a different time course. These results suggest that the information about the multiple components of value signals is dynamically routed throughout the frontostriatall network during strategic planning.

Disclosures: M. Park: None. **J. Lei:** None. **M. Oemisch:** None. **H. Liang:** None. **B. van Opheusden:** None. **W. Ma:** None. **D. Lee:** None.

Poster

PSTR132: Prefrontal Cortex in Non-Human Primates

Location: MCP Hall A

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Program #/Poster #: PSTR132.14/J29

Topic: H.03. Decision Making

Support: NIH R01 DA047870
NIMH ZIA MH002928

Title: Dynamic model arbitration through alignment of learned values with choice and reward subspaces in prefrontal cortex

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Abstract: One of the hallmarks of higher cognitive function is the ability to link outcomes to relevant features of the environment, while ignoring the irrelevant features. This is especially challenging for naturalistic settings, where any features or attributes of a selected option can be predictive of rewards. It has been suggested that the brain tackles such uncertainty by running multiple internal models of the environment and arbitrating among them based on their reliability. To study the neural mechanisms underlying this dynamic arbitration process, we carried out high channel count recordings in dorsolateral prefrontal cortex (dlPFC) while monkeys performed a probabilistic reversal learning task with additional uncertainty about the correct reward mappings for each block (stimulus- vs. action-based). To explain choice behavior, we devised multiple reinforcement learning (RL) models with reliability-based arbitration between stimulus- and action-based learning systems, and found evidence for dynamic, competitive interaction between two systems. Next, we used linear regression to examine single-unit activities in dlPFC. The predictors included task-related variables and RL-estimated signals including arbitration weight, the value difference within each learning system (ΔV_{Stim}, ΔV_{Act}), and the chosen values ($V_{C,Stim}$, $V_{C,Act}$). We found that dlPFC was involved in arbitration in two ways: (1) arbitration weight was represented in the activity of dlPFC neurons significantly above chance level (binomial test, $P<.001$); (2) only the relevant value information for the currently adopted strategy were encoded congruently with subsequent choice and reward. That is, after cue onset and before choice, the correlation between regression coefficients for choice and ΔV_{Stim} were high when stimulus system was dominant (Spearman's $r=.40$, $P<.001$), more so than between choice and ΔV_{Act} ($r=0.15$, $P<.001$). Conversely, the coefficients for choice and ΔV_{Act} were significantly correlated when action system was dominant ($r=.21$, $P<.001$), while those for choice and ΔV_{Stim} were not ($r=.04$). Similarly, after reward feedback, regression coefficients for (previous) reward and $V_{C,Stim}$ were highly correlated during stimulus-dominant trials ($r=.41$, $P<.001$), as those for reward and $V_{C,Act}$ were during action-dominant trials ($r=.37$, $P<.001$). These results suggest that the population subspaces for values in relevant learning system were dynamically aligned with those for choice and reward according to the currently adopted strategy. Together, our results suggest that dlPFC may be crucial for flexible arbitration between competing models of the environment.

Disclosures: J. Woo: None. **M.C. Wang:** None. **R. Bartolo-Orozco:** None. **B.B. Averbeck:** None. **A. Soltani:** None.

Poster

PSTR132: Prefrontal Cortex in Non-Human Primates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR132.15/J30

Topic: H.03. Decision Making

Support: BRI Carol Moss Spivak Fellowship
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Title: The effects of optical inhibition of anterior cingulate cortex in information and effort-based choices

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Abstract: Subjects are often willing to pay a cost for information. This is clear in a task that promotes paradoxical choices. Here, rats choose between a lever associated with a cue that results in a larger reward 50% of the time (S_0, No Info) vs. a lever that is followed by one of two cues that signal certain outcomes (Info): one always leading to a smaller reward 100% (S+) and the other never rewarded, 0% (S-). Overall, the more profitable option is to choose the S_0 that leads to more reward. However, rats (and humans) usually choose the lever associated with the cues that possess more information, despite being less profitable. We previously found that chemogenetic inhibition of the anterior cingulate cortex (ACC) destabilized choice preference without affecting latency to choose or response rate to cues (Gonzalez et al., 2024). This effect on information choices spanned sessions, yet did not reveal if there was a key trial epoch that required ACC for these choices. In the present experiment, Long-Evans rats (n=22, 13 females) were prepared with either bilateral archaerhodopsin (ArchT-Green) or administered an eYFP virus on a CaMKIIa promoter in ACC (0.3 µL at 0.1 µL/min AP: +3.7, ML: ±0.8, DV: -2.4 for a total volume of 0.3 µL per side), followed by the implantation of optic fiber ferrules in this region (inserted at a 15° angle same AP and ML, DV = -2.2). Rats were trained to stable preference and then tested over 5 sessions with optical inhibition at distinct trial epochs, in counterbalanced order: inhibition during the presentation of the S+ cue in two sessions, during Info vs. No Info choice in one session, and during 10% of the 10-sec intertrial intervals in two other sessions. Baseline sessions (no laser was used) occurred between these manipulations. Again, we observed no changes in latency to choose or response rate to the cues during any of the manipulations, consistent with findings from our previous chemogenetic study (Gonzalez et al., 2024). However, unlike chemogenetic inhibition of ACC, no changes in choice preference were observed following optogenetic inhibition during any epoch (mixed-effects GLM, $p > .05$). To confirm the efficacy of optical inhibition of ACC, rats were tested on a progressive ratio (PR) and PR with a choice of chow (PRC) procedures similar to previous work (Hart et al. 2017; Hart et al., 2020). Optical inhibition of ACC during reward retrieval reduced breakpoints in both PR and PRC conditions (t-tests, p's $< .05$). Collectively, these experiments support the idea that ACC may serve a higher-order role in tracking and perhaps integrating value in Info choices based on acquiring information across sessions, rather than a role at particular timepoints during the session.

Disclosures: V.V. Gonzalez: None. **M. Malvaez:** None. **M. Sharpe:** None. **K.M. Wassum:** None. **A. Izquierdo:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Topic: H.03. Decision Making

Support: NIMH Grant R01MH110822
NIMH Grant R01MH132064

Title: Subregion encoding of decision variables and underlying communication within macaque ventral frontal cortex

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Abstract: The ventral frontal cortex (VFC) in macaques is involved in numerous affective and cognitive processes, from multimodal sensory integration to the selection and use of internal and external features to flexibly guide decision-making. VFC is composed of a heterogeneous set of subregions, encompassing many subdivisions within the orbitofrontal cortex, ventrolateral cortex, and anterior insula. Based on the interconnections between these subregions, prior anatomical work revealed the existence of multiple networks within VFC. It is unclear, however, whether specific functions map onto these known anatomical subregions, in part, because prior studies have lacked the resolution to test for difference. Here we recorded the activity of thousands of neurons across large portions of VFC in monkeys performing a two-choice probabilistic task for different fruit juices outcomes. We then compared encoding to precise post-mortem neuroanatomical parcellations to investigate the differences in neural encoding and communication between 8 distinct cytoarchitectonic areas in VFC. We found that the ventrolateral area 12l, not 12o, represented multiple choice attributes when monkeys evaluated the options presented to them, while orbitofrontal area 11m/l contained more specific representations of the quality of the outcome that could be earned. We also found a highly distributed reward delivery encoding across all VFC subregions, while the reward properties were more specifically observed in areas receiving gustatory inputs, notably 11m/l and 13m. Further, the onset of stimuli and reward globally increased communication within all ventral frontal cortex, with area 12l/o showing the highest connectivity with other areas. Responses in 12l/o were often preceded by responses in other subregions, suggesting a critical integrative role for these areas in decision-making. Taken together, our work highlights the diversity of encoding and communication within the various subregions of VFC.

Disclosures: F.M. Stoll: None. **P.H. Rudebeck:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Pew Biomedical Scholars Program
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Decision making in the context of multi-attribute options

Authors: *A. PERKINS[1], E. L. RICH[2];
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Abstract: Often decisions are made between options that have multiple features, or attributes, that are relevant to one's choice. For example, when deciding between snacks to purchase, one might factor cost and taste into a selection. The orbitofrontal cortex (OFC) has an important role in decision-making and OFC neurons represent associations between stimuli and their overall values. However, it is still unknown whether OFC only evaluates options on the basis of their integrated value, as suboptimal decision-making effects such as the attraction effect indicate that within-attribute comparison may also contribute to decision-making. To investigate how multi-attribute options are represented in neural activity, we trained two rhesus macaques on a multi-attribute decision making task, in which two simultaneously-presented options were represented by stimuli reflecting the sweetness of that option's sucrose reward, and the probability of receiving that reward. These composite stimuli represented information about the attributes of the options with separate bars that either increased or decreased with increasing attribute value, allowing us to investigate both free-viewing gaze behavior and changes in choice behavior due to perturbations in attribute presentation. We recorded neurons in OFC and frontal eye fields (FEF) using acute electrodes and multi-contact linear probes. We found that when comparable attributes did not share a presentation mode (e.g., reward bar A increased in size with increasing sweetness, while reward bar B decreased), choice behavior became suboptimal, implying a role for within-attribute comparison. Likewise, analysis of gaze transitions reveals a preference for within-attribute over within-option comparisons. Neuronal analysis indicates a greater presence of independent information relating to attribute than integrated value of the chosen option in OFC and FEF firing rates, and that representations of the attributes of the fixated option were "broken apart" in OFC but correlated in FEF. Our results support the notion that value-based decisions take place, at least partially, in the space of individual attributes, and may depend on attribute value representations in OFC.

Disclosures: A. Perkins: None. **E.L. Rich:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: H.03. Decision Making

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KAKENHI JP19H05467
KAKENHI JP20H05955
JST PRESTO JPMJPR22S3
JST PRESTO JPMJPR2128
AMED JP23dm0307007
AMED JP21dm0107146
AMED JP20dm0307021
AMED JP21dm0207077
NBRP Japanese Monkeys

Title: Distinct roles of monkey OFC-subcortical pathways in adaptive behavior

Authors: *K. OYAMA[1], K. MAJIMA[1], Y. NAGAI[1], Y. HORI[1], T. HIRABAYASHI[1], M. A. ELDRIDGE[2], K. MIMURA[1], N. MIYAKAWA[1], A. FUJIMOTO[3], Y. HORI[1], H. IWAOKI[1], K.-I. INOUE[4], R. C. SAUNDERS[2], M. TAKADA[4], N. YAHATA[1], M. HIGUCHI[1], B. J. RICHMOND[2], T. MINAMIMOTO[1];
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Abstract: Primates must adapt to changing environments by optimizing their behavior to make beneficial choices. At the core of adaptive behavior is the orbitofrontal cortex (OFC), specifically Brodmann's area 11/13, of the brain, which updates choice value through direct experience or knowledge-based inference. Subcortical structures, such as the rostromedial part of the caudate nucleus (rmCD) and the medial part of the mediodorsal thalamus (MDm), receive direct projections from the OFC, and are thought to be also involved in such adaptive behavior. However, the causal contributions of these areas and neural pathways connecting them to these different value-updating strategies remain unidentified in primates. In this study, we used a chemogenetic tool, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), to reversibly silence the activity of the OFC and to suppress synaptic transmission from the OFC to two subcortical areas. We designed two behavioral tasks in which two male macaque monkeys updated the values of certain items, either by directly experiencing changes in stimulus-reward associations, or by inferring the value of unexperienced items based on the task's rules. Chemogenetic silencing of bilateral OFC through systemic injection of agonists, deschloroclozapine, combined with the analysis fitting the data with reinforcement learning models revealed that monkey OFC is causally involved in updating item value based on both experience and inference. In vivo imaging of chemogenetic receptors by positron emission

tomography allowed us to map projections from the OFC to the rmCD and MDm. Chemogenetic silencing of the OFC-rmCD pathway through local infusion of agonists at axonal terminals impaired experience-based value updating, while silencing the OFC-MDm pathway impaired inference-based value updating. Our results thus demonstrate dissociable contributions of distinct OFC-subcortical projections to different behavioral strategies, and provide new insights into the neural basis of value-based adaptive decision-making in primates.

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Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

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Program #/Poster #: PSTR133.04/J34

Topic: H.03. Decision Making

Support: National Science and Technology Innovation 2030 Major Program, Grant No. 2021ZD0203700/2021ZD0203702

Title: Prefrontal mechanisms of value working memory mediated economic decisions

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Abstract: Working memory and value-based decision-making are foundational aspects of cognition, and a wealth of research has established a causal connection between the prefrontal cortex and these cognitive functions. However, the neural mechanisms underlying value working memory (vWM) and vWM-mediated choices remain poorly understood. In this study, we trained two monkeys to perform an economic choice task with sequentially presented offers (consisting of offer 1, memory, and offer 2 periods), requiring the memorization of offer 1's value for subsequent comparison with offer 2 to make a choice. The task introduced variations in offers' attributes, including their order, location, and preference for juice type, allowing for choices to be made in three potential reference frames: order, space, and taste. Using multi-channel recordings, we recorded approximately 2600 neurons from both the orbitofrontal cortex (OFC) and lateral prefrontal cortex (LPFC). Our analysis focused on identifying neuronal representations of offer values in different task phases and choice signals in different reference frames. We found that while only a few neurons exhibited persistent value-selective activity in either area, pseudo-population decoding analysis revealed maintenance of offer 1's value in WM

and its retrieval during the offer 2 period in both brain regions. A cross-temporal decoding analysis further demonstrated stable and significant coding for economic values during the WM period, with dynamic coding more prevalent outside the WM period. Moreover, we observed notable differences between the OFC and LPFC. Firstly, OFC exhibited stronger value coding strength during the encoding phase, while LPFC showed more sustained encoding during the memory phase. Secondly, choice signals indicated an earlier initiation and dominance of choice in the order reference frame in OFC, followed by choice signals in the order and space reference frames in LPFC. Weak and delayed choice signals were observed in the taste reference frame in both regions. Lastly, the encoding of offer value 2 was much stronger in OFC than in LPFC. These results suggest that in vWM-mediated choice, LPFC is preferentially engaged in encoding value working memory, while OFC is more involved in decision-making processes themselves.

Disclosures: K. Ni: None. **X. Cai:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Topic: H.03. Decision Making

Support: National Science and Technology Innovation 2030 Major Program, Grant No. 2021ZD0203700/2021ZD0203702

Title: Attribute integration demand shapes the temporal evolution of decision-related signals in the orbitofrontal cortex

Authors: *Y. PENG[1,2], C. XU[1,2], X. CAI[2,3];
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Abstract: Attribute integration demand shapes the temporal evolution of decision-relatedsignals in the orbitofrontal cortex
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AbstractInvestigations into the neural substrates of economic decision-making have highlighted the orbitofrontal cortex (OFC) as a key brain region that encodes subjective values for decision processes. Emerging evidence from anatomical and experimental studies suggests that the OFC contributes to value-based decisions, particularly when integrating multiple attributes is necessary. To further examine this proposition, we trained two monkeys to perform an economic

choice task that incentivized the integration of multiple decision attributes (Multiple-attribute integration, MI), alongside a variant discouraging such integration (Single-attribute dominant, SD). Both tasks presented options comprising two decision attributes: reward quantity and juice type, albeit differing in demand for attribute integration. In the MI task, subjects were required to integrate both juice type and reward quantity to maximize reward, whereas in the SD task, selecting the option with greater quantity, irrespective of juice taste, sufficed for value maximization. This experimental design afforded subjects different decision contexts, enabling assessment and comparison of neuronal activity under varied computational demands for attribute integration, while preserving task structure and option attributes. Using multi-channel recordings, we recorded over 1835 neurons from the OFC of two animals across two tasks. We then trained decoders on the neural activities of the OFC pseudo-populations to explore the temporal characteristics of decision-related signals. Analysis of temporal differences in task-related variables shows that when attribute integration demand is high, the decision-related signals are significantly less synchronized, and the choice signals are more delayed. These results suggest that the time course of decision-related signals in the OFC reflects the attribute-integration process during economic decision-making, thus lending further support to the notion that OFC plays a pivotal role in subjective value computation.

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Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Topic: H.03. Decision Making

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Title: Ketamine impairs working memory but not reward-based decisions

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Abstract: Ketamine, which has been increasingly used for its rapid antidepressant effects, also poses potential cognitive deficits. Working memory and decision-making are fundamental cognitive functions often suggested to share a common neural mechanism. While studies have revealed ketamine's disruption of mental representations in the primate lateral prefrontal cortex (LPFC), particularly in spatial working memory, its influence on reward-based decisions remains

underexplored. To further investigate ketamine's impact on memory and decision-making, we trained two monkeys in a reward-based decision-making task with sequentially presented offers (SRD task). In this task, offer 1 is presented for 1 second, followed by offer 2 with a 1-second memory period in between. To maximize reward, the animals need to remember the amount of the first offer for subsequent decisions. To test ketamine's effects, we conducted sessions under three conditions on different experimental days: 1) Control (no injection, 29 sessions); 2) Ketamine (IM injection, subanesthetic doses, 0.2-0.5 mg/kg, 28 sessions); 3) Saline (IM injection, 24 sessions). While no performance differences emerged between Control and Saline conditions, Ketamine exposure prompted increased errors in choosing the smaller amount when the two offer amounts were close. These errors were accompanied by the animals' biased choice towards the second offer that does not require maintenance in working memory. In both animals, this effect peaked 5-20 minutes post-ketamine injection. These behavior outcomes are consistent with deficits in working memory. To assess ketamine's influence on decision-making independent of working memory, we modified the SRD task. We presented the second offer before the first offer's disappearance with a 500ms overlap, thus eliminating the working memory component. Under this non-memory version, ketamine did not impact choice patterns. Hence, in our study, ketamine was found to impair the representation of value in working memory without affecting the processing of rewards or the decision-making process itself.

Disclosures: Y. liu: None. **K. Ni:** None. **X. Cai:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.07/J37

Topic: H.03. Decision Making

Support: ISF Grant

Title: Top-down orbitofrontal cortex projections mediate neuronal probability estimation in the piriform cortex

Authors: *T. DALAL[1], R. HADDAD[2];
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Abstract: Estimating the statistics of events occurring around us is a crucial feature for survival. However, how the brain encodes and updates these internal probability distributions, and at which processing level, is poorly understood . Here, we devised an odor-discrimination task in which mice could utilize preceding odor cues to estimate the probability of encountering a subsequent odor. Recording the neural activity in the primary olfactory cortex, we found two non-overlapping neuronal subpopulations that encode the odor probability contingencies differentially. One subpopulation exhibited informative activity on the probability of the upcoming odor before it arrived, and the other subpopulation signaled the stimulus prediction

error when it arrived. Bilaterally silencing the orbitofrontal cortex hampered mice's ability to utilize the cue-probability contingencies and eliminated its neuronal correlates in the piriform cortex. However, it did not affect the prediction error signals. These findings shed light on how the brain generates events-related probability distributions and suggest that sensory activity is biased by prior beliefs.

Disclosures: T. Dalal: None. **R. Haddad:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Topic: H.03. Decision Making

Support: NIH grant DA051598
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NIH grant MH129320
NIH grant DA018343

Title: Adolescent decision-making trajectories are associated with orbitofrontal perineuronal nets

Authors: *M. M. BONILLA[1], S. M. GROMAN[2];
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Abstract: Age-related improvements in decision-making during adolescent may be associated with select neurodevelopmental mechanisms. Although the identity of these mechanisms is not known, evidence indicates a key role of orbitofrontal circuits. We recently discovered that decision-making functions in adolescence were correlated with the abundance of proteins known to be involved in the formation of perineuronal nets (PNNs). PNNs are extracellular matrix structures involved in the stabilization of neural circuits, we hypothesized that age-related increases in the density of perineuronal nets within the orbitofrontal cortex may mediate adolescent decision-making trajectories. To test this hypothesis, decision-making functions were assessed throughout adolescence in male and female Long Evans rats (N=63) using a three-choice, probabilistic reversal learning task. Brain tissue was collected at different adolescent ages (P30, P50, and P70) and PNNs stained using Wisteria floribunda agglutinin (WFA). The density and size of PNNs in the orbitofrontal cortex was quantified in each individual rat using ImageJ and compared across ages (P30-P70), sexes, and with decision-making measures. We found that performance in the reversal learning task improved across adolescence in both male and female rats and that this was due to age-related increases in reward updating mechanisms (R^2=0.20). The density and size of PNNs within the orbitofrontal cortex increased along the anterior-posterior gradient as well as changing as a function of age. Performance in the reversal learning task was not correlated to PNN density but with PNN size in a sex-specific manner, suggesting there may

be sex differences in the maturation of decision-making circuits. These data suggest that formation and maturation of perineuronal nets within the orbitofrontal cortex may be critical in the development of decision-making functions which we have found to be important mediators of addiction susceptibility. Future studies will test this hypothesis and determine the impact of degrading orbitofrontal PNNs on adolescent decision-making trajectories and drug-taking behaviors.

Disclosures: M.M. Bonilla: None. **S.M. Groman:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.09/K2

Topic: H.03. Decision Making

Support: NIH Grant ZIA-DA000587
NIH Grant ZIA-MH002983
JSPS Overseas Research Fellowship 020157

Title: The orbitofrontal cortex integrates correlated features of expected outcomes into unitary constructs

Authors: *A. SHIMBO[1], Y. K. TAKAHASHI[1], A. J. LANGDON[2], T. A. STALNAKER[1], G. SCHOENBAUM[1];
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Abstract: The orbitofrontal cortex (OFC) is crucial for tracking various aspects of expected outcomes, including their size, timing, and unique sensory features. This information plays a role in guiding our choices and supports learning when actual outcomes diverge from these expectations through its influence on dopaminergic prediction errors. A previous study showed that the effects of reward timing and size on activity in single units in OFC were dissociable, with largely separable populations of neurons responding to one or the other variable, in an odor-guided choice task in which they were manipulated independently (Roesch et al, Neuron, 2006). However, in real-life decision-making scenarios, outcome features often change simultaneously, so here we asked how OFC neurons would represent information about the timing an expected reward, in the same choice task, but under conditions in which changes in timing were sometimes confounded with changes in identity. Specifically in some trial blocks, when the timing of the reward changed, its flavor also changed, as if a different reward was being delivered, whereas in other blocks, the timing changed but the flavor remained the same, as if a single reward was being moved. Under these conditions, a substantial number of OFC neurons fired differentially to immediate versus delayed reward and also to the different reward flavors. However, contrary to the previous study, encoding of reward timing was strongly correlated with

selectivity for reward identity. Taken together with the previous research, these results indicate that when reward features are correlated, OFC tends to integrate them into unitary constructs, whereas when they are independent, OFC tends to segregate them into separate constructs. In addition to this result, we also found that when both reward timing and identity changed, some OFC neurons initially showed unique activity leading up to and during the missing reward, differences that were not evident when only timing changed. Notably this OFC activity mirrored and slightly preceded that observed in ventral tegmental area dopamine activity in a previous study (Takahashi et al., Nature Neuroscience, 2023). The current data imply that OFC might convey predictions to VTA that track reward timing separately based on reward identity.

Disclosures: A. Shimbo: None. **Y.K. Takahashi:** None. **A.J. Langdon:** None. **T.A. Stalnaker:** None. **G. Schoenbaum:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

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Topic: H.03. Decision Making

Support: NIH Grant 5R00DA036561
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Concordia Univ. start-up funds

Title: Orbitofrontal neurons encode both the relative and absolute predictive credit of reward cues

Authors: *M. KANG[1,3], N. TU[3], K. KAUFMAN[4], S. G. VOLZ[3], F. ALHAZMI[2], I. REVERTE[5], M. P. GARDNER[6], M. D. IORDANOVA[7], G. ESBER[8];
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Abstract: Our behavior is constantly guided by environmental cues that predict important outcomes, yet how such cues acquire predictive credit remains poorly understood. Ample behavioral evidence suggests that predictive credit is not merely a function of how well the cue predicts the outcome by itself, but by comparison with other cues, suggesting predictive credit is determined by the cue's relative rather than absolute validity. However, growing evidence indicates that under a variety of training conditions cue-evoked behaviors reflect the cue's absolute validity. Moreover, marked differences in how individuals assign predictive credit have been reported in clinical and healthy populations. For this reason, it has been suggested that relative and absolute credit assignment should be considered as the extremes of a learning

continuum. Here, we investigated the role of the lateral orbitofrontal cortex (lOFC) in this continuum. While the lOFC has long been implicated in signaling cue-related predictive information about impending rewards, it is unclear whether orbitofrontal neurons track the relative or absolute validity of cues. To examine this question, we designed a behavioral task in which net relative and net absolute credit assignment are behaviorally expressed as opposite patterns of responding to two target cues. We recorded single-unit activity in rats previously selected for showing a net relative or absolute credit assignment profile. We found that distinct subpopulations of lOFC neurons track the relative and absolute validity of cues regardless of whether the animals' behavior predominantly reflect relative or absolute credit assignment. However, the relative proportions of these subpopulations correlated with the individual's behavioral profile. Interestingly, opto- and chemogenetic inhibition of lOFC facilitated relative credit assignment. Our findings suggest that the brain tracks both the relative and absolute validity of cues, and sheds new light on the role of the lOFC in credit assignment.

Disclosures: M. Kang: None. **N. Tu:** None. **K. Kaufman:** None. **S.G. Volz:** None. **F. Alhazmi:** None. **I. Reverte:** None. **M.P. Gardner:** None. **M.D. Iordanova:** None. **G. Esber:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.11/K4

Topic: H.03. Decision Making

Support: AdERC grant GA-340063

Title: Neural correlates of rapid learning in the Orbitofrontal cortex

Authors: *M. KARAYANNI[1], M. M. JANKOWSKI[2], Y. LOEWENSTEIN[3], I. NELKEN[4]; [1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Edmond and Lily Safra Ctr. for Brain Sci., Gdańsk Univ. of Technol., Gdansk, Poland; [3]Edmond & Lily Safra Ctr. for Brain Sci., Hebrew Univ., Jerusalem, Israel; [4]Hebrew Univ., Jerusalem, Israel

Abstract: Few-shot, rapid learning, enables us to swiftly grasp new knowledge and skills with little guidance or reinforcement. Computational studies emphasize the importance of abstract representations and generalization to rapid learning. Previous studies have revealed both correlative and causal relationships between the Orbitofrontal cortex (OFC) and these essential features of rapid learning. To directly investigate OFC with rapid learning, we developed a behavioral task that tests learning strategies in freely-moving rats. To succeed in this task, the rat had to discover the correct sequence of two pokes (each out of six possible ports). Poking in the correct port resulted in visual and auditory feedback, and any mistake resulted in a reset to the beginning of the task. After pokes into the two ports forming the correct sequence, a third poke in any port resulted in reward. Rats exhibited rapid learning, with near-optimal performance after

1-2 rewards, so that the correct sequence could be changed up to 10 times in a single session. The rats used hierarchical problem-solving strategies, leveraging their knowledge of the task structure. Untethered Neuropixels recordings from the OFC demonstrated heterogeneous yet robust responses around task-related events, giving rise to rich task-related representations. These representations were found to be modulated by the task state and by the stage of learning of each sequence.

Disclosures: M. Karayanni: None. **M.M. Jankowski:** None. **Y. Loewenstein:** None. **I. Nelken:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Program #/Poster #: PSTR133.12/K5

Topic: H.03. Decision Making

Support: NIH Grant T32-DA037183

Title: A triple dissociation across the medial, ventral, and lateral orbitofrontal cortex in rats making sequential foraging decisions

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[1]Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN; [2]Dept. Neurosci, Univ. of Minnesota, Minneapolis, MN

Abstract: Diverse roles have been suggested for the rat orbitofrontal cortex (OFC) in economic decisions. However, the OFC is heterogenous and it is unclear how the OFC's diverse roles change with that heterogeneity. To address this issue, we recorded neural ensembles across the medial (MO) to ventral (VO) to lateral (LO) span from three simultaneously implanted silicon probes in rats performing the Restaurant Row neuroeconomic task.
Rats earned their daily food intake on a time-limited budget by foraging for sequentially encountered delayed rewards. Rats made an initial accept/reject decision in the "offer zone" (OZ), where a tone signaled reward delay for that offer (1-30 s). If the offer was accepted by entering a "wait zone" (WZ), the delay counted down and rats could wait out the delay or reevaluate their initial decision by quitting to go to the next restaurant. Rats learned to reject long-delay offers while accepting short-delay offers in the OZ. If long-delay offers were mistakenly accepted in the OZ, rats often quit the WZ.
In the OZ, LO ensembles showed an initial burst followed by sustained activity that was greater for better offers. VO activity rose with time spent in the OZ. This rise was steeper for worse offers. LO and VO provided opposing signals during OZ decisions, such that LO > VO when accepting, but VO > LO when skipping. MO activity increased just prior to leaving the OZ regardless of decision. Importantly, OZ neural dynamics across the OFC appeared only after behavioral adaptations to a reward scarce environment.

In the WZ, LO ensembles increased as time to reward approached. VO activity was elevated in the WZ before quits, and burst when the quit decision was made. Opposing neural dynamics during reevaluation between LO and VO again resulted in LO > VO when earning reward, but VO > LO when quitting. MO activity bridged the transition from OZ to WZ and remained active only if the offer was quit.
Finally, previous work using a variant of Restaurant Row found that moments of "regret" (i.e., skipping a good offer only to encounter a bad offer) were associated with 1) stronger propensity for approach decisions, and 2) representations of regret-inducing decision locations in lateral aspects of OFC. We replicated these findings in LO, but found no regret-related representations in VO or MO.
Collectively, these results are consistent with the hypothesis that LO encodes the subjective value of current rewards, along with regretful experiences, to govern approach decisions. In contrast, VO encoded the subjective value of future offers (opportunity costs) to override approach temptations driven in the LO. MO was involved in monitoring valuations to help correct bad decisions.

Disclosures: P.J. Cunningham: None. **A.D. Redish:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR133.13/K6

Topic: H.03. Decision Making

Title: Orbitofrontal responses on a continuous spatial bandit task

Authors: *S. GUPTA[1], C. CUETO[2], F. ABZUN ERAZO[1], A. REBOLLAR[1], S. MANSUR[1], A. LOK YUNG YONG[1], A. M. WIKENHEISER[1];
[1]Psychology, UCLA, Los Angeles, CA; [2]California State Univ., San Bernardino, San Bernardino, CA

Abstract: The orbitofrontal cortex (OFC) is important for reward processing and has been implicated in representing the subjective value of available options during an impending decision. In rodent paradigms, a notable proportion of OFC neurons signal the direction subjects will move on each trial to indicate their choice; such response direction coding occurs both independent of and entangled with value representations at the level of single neurons. Neural recordings from rodent OFC in open-field paradigms show that many neurons have weak allocentric spatial response correlates. Thus, in contrast with data from primates, in which evidence of spatial or response correlates in OFC neurons is mixed, the rodent OFC frequently multiplexes such information along with other representations. However, it is difficult to fully characterize the nature of OFC spatial responses in recordings made in operant boxes, where allocentric space, egocentric space, and action representations are largely confounded. To better understand rat OFC representations during decision making, we designed a novel behavioral

paradigm in which the probability of reward varies across space in a structured—but uncued—way. Rats (n = 11; 5 female) approached and paused at visual stimuli projected on the floor of an open field arena; reward was delivered probabilistically based on the location of the stimulus rats chose following a latent probability map that assigned higher and lower reward probabilities to distinct locations in the arena. Preliminary data shows rats' decisions were driven by the underlying reward-probability map; as the difference in value between stimuli increased, rats favored the higher-probability option. High-density neural recordings from lateral OFC (n = 2 rats; 1 female) show that ensembles form a spatially-invariant representation of trial epoch. Reward delivery and chosen value can be decoded from the OFC activity as rats are choosing a stimulus but before the outcome of the trial is revealed, though preliminary analyses are consistent with a relatively coarse representation of value compared with previous reports of OFC neurons. Preliminary analyses of the spatial tuning curves show weak correlation in spatial tuning between the trial and ITI periods, despite firing rates being largely stable.

Disclosures: S. Gupta: None. **C. Cueto:** None. **F. Abzun Erazo:** None. **A. Rebollar:** None. **S. Mansur:** None. **A. Lok Yung Yong:** None. **A.M. Wikenheiser:** None.

Poster

PSTR133: Decision-Making: Orbitofrontal Cortex

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Topic: H.03. Decision Making

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T32MH015174

Title: Flexible value computation in mouse orbitofrontal cortex, and the role of hippocampal input in contextual learning

Authors: *A. GUNGI[1], K. IIGAYA[1], K. KUMAR[2], C. ANACKER[3];
[1]Columbia Univ., New York, NY; [2]Columbia Univ., Brooklyn, NY; [3]Psychiatry, Columbia Univ., New York, NY

Abstract: Animals must learn to navigate rich worlds filled with multiple salient features, and identify relevant ones to obtain rewards optimally. However, the neural mechanisms underlying this flexible computation of the value of features are not well understood. Here we analyze behavioral and neural data from medial orbitofrontal cortex (mOFC) while intervening on ventral hippocampus (vHPC) input in mice performing a naturalistic decision-making task, involving tracking multiple feature sets (odor, texture, direction) and assigning dynamical value to each of them. The animals had to learn changing value across the same axis (odor A to odor B) and across unrelated axes (odor A to texture B). We developed a novel method, called

Representational Evolution Analysis (REA), to examine how the neural representations of feature values evolve across time. Using REA, we test a novel hypothesis of the role of vHPC input on flexible decision-making, namely that the vHPC input to the mOFC regulates context, and enables the same populations of neurons in the mOFC to be used to code the same features, enabling flexible reversal. vHPC input inhibition is expected to inhibit this type of contextual learning and our study offers insight into the underlying neural mechanisms. This is in line with other hypotheses of hippocampal function that also postulate that the hippocampus is responsible for learning models of the world, and manipulating those models in similar contexts for flexible cognition.

Disclosures: A. Gungi: None. **K. Iigaya:** None. **K. Kumar:** None. **C. Anacker:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.01/K8

Topic: H.03. Decision Making

Support: NIH Brain Initiative F32 1F32MH132176-01

Title: The role of orbitofrontal cortical projections to the striatum for value-based decision-making.

Authors: *M. L. DEMAEGD, J. SCHINDLER, C. M. CONSTANTINOPLE;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: We sought to characterize the role of orbitofrontal cortex (OFC) projections to the striatum in value-based decision-making. Because subregions within the striatum have distinct influences on behavior, we initially determined whether overlapping or distinct populations of OFC neurons projected to different subregions. Using retrograde tracers (cholera toxin subunit B) injected in different striatal subregions, we found that individual neurons in the lateral OFC project either to the dorsolateral striatum (DLS) or ventral striatum (VS) with very little overlap between these projection classes.
We then used a combination of optogenetics and electrophysiology to record from and manipulate these projection-specific OFC neurons while rats performed a value-based decision-making task. Our lab has developed a temporal wagering task in which rats choose to wait for one of five volumes of water reward, cued by an auditory tone. There is a latent block structure in which the rat experiences blocks of trials with differing reward statistics, which systematically affect how long rats are willing to wait for rewards. We used viral methods to express channelrhodopsin (ChR2) selectively in either DLS or VS projecting OFC neurons and implanted Neuropixels probes in OFC and fiber optics over their axon terminals in the striatum. On a subset of trials on optogenetic sessions we activated these projections when the animal received its reward and evaluated effects on behavior. Our preliminary findings show that

manipulating OFC-DLS, but not OFC-VS neurons, affects how long rats are willing to wait for rewards. Computational modeling and complementary analyses suggest that manipulating this projection might change rats' beliefs about the current block.
We next recorded from optogenetically-tagged projection neurons in OFC while optically eliciting antidromic action potentials in their striatal terminals. Projection neurons were identified using collision tests. Neurons projecting to DLS showed heterogeneous temporal response profiles but similar encoding of evidence for high reward contexts, namely encoding of high-volume rewards modulated by the reward block. These results lay a foundation for understanding how distinct output pathways from OFC interact with downstream circuits to coordinate value-based decisions.

Disclosures: M.L. DeMaegd: None. **J. Schindler:** None. **C.M. Constantinople:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.02/K9

Topic: H.03. Decision Making

Support: NIH Brain Initiative F32-1F32MH132176-01

Title: Distinct populations of orbitofrontal cortex neurons in rats individually project to subregions of the stratum and midbrain

Authors: *J. SCHINDLER[1], M. DEMAEGD[2];
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Abstract: The orbitofrontal cortex (OFC) is known to play a key role in value-based decision-making. Consistent with this, OFC neurons project to several downstream structures that are critical for reward learning and action selection, including the ventral tegmental area (VTA) and ventral and dorsal striatum. Because studies of OFC projections often focus on either gross targeting throughout the brain or specific targeting of single downstream regions, the spatial distribution and overlap of projections to distinct regions has not been well characterized. Here, we test whether OFC neurons targeting different subcortical circuits are partially overlapping vs. distinct populations. First, we used cholera toxin subunit B (CTB) to retrogradely label OFC neurons targeting distinct brain regions in rats. By injecting CTBs conjugated to different fluorophores into different subregions in the same animal, we found that largely non-overlapping subpopulations of OFC neurons projected to distinct striatal and midbrain targets. Neurons projecting to ventral striatum, dorsal striatum, and VTA were all localized in different subregions and layers of the OFC. Projections to the ventral striatum were found in lateral OFC and agranular insula (AI), and were localized to superficial cortical layers. Dorsomedial striatum projection-neurons were localized to deep layers of the ventral and medial OFC (MO/VO), while dorsolateral striatum projection-neurons were found in deep layers of the ventral OFC, lateral

OFC (LO), and AI. Projections to the VTA were found across the medio-lateral axis and localized to intermediate (putatively superficial layer 5) cortical layers. We corroborated results from retrograde tracing experiments using anterograde tracing and electrophysiology. Our data indicate that distinct populations of OFC neurons project directly to the dorsal striatum, ventral striatum, and VTA individually. Altogether, characterizing these projection patterns is critical to understanding the logic of top-down OFC projections and how information relevant to decision-making and learning is routed through the mammalian brain.

Disclosures: J. Schindler: None. **M. DeMaegd:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.03/K10

Topic: H.03. Decision Making

Support: Junior Simons Fellow

Title: Novel task to estimate temporal discounting in rats

Authors: *A. C. MARTIN, C. E. M. GOLDEN, C. M. CONSTANTINOPLE;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Animals must learn to maximize reward for survival in complex environments, where rewards materialize on both short and long timescales. Multiple species prefer smaller rewards that arrive sooner instead of larger rewards to be delivered later, termed temporal discounting. The subjective value of future rewards is commonly discounted in a hyperbolic manner, where the value of the reward is inversely proportional to its delay and discounted more rapidly for shorter delays. The rate at which rewards are discounted in time varies by individual. To measure individual discount rates in rats and determine whether they exhibit hyperbolic discounting, we developed an intertemporal choice task, inspired by Kobayashi and Schultz, 2008 where water-restricted rats chose between a smaller volume of water reward delivered sooner (SS) or a larger reward delivered later (LL). The delay length of the SS choice was always 0.5 s, while the volume of reward varied between 4, 8, 16, 32, or 40 µl. The LL choice was always 40 µl, but the delay length varied between 1, 2, 4, or 8 s. An equally likely choice of SS and LL implied that the two options were subjectively equivalent, providing a behavioral read-out of the temporally discounted LL value. The rat initiated each trial by poking its nose in a center port, which triggered lights to turn on in two side ports. The SS and LL rewards were always associated with the same side port for each rat, and the locations were counterbalanced across rats. After selecting their choice via a nose poke in the associated port, auditory tones of descending pitch frequencies played every 250 ms until the delay ended and reward was delivered. The SS and LL choice combinations were randomly and independently presented in blocks of trials so that all 20 combinations of reward volumes and delays were possible. Each block began with five forced

choice trials to communicate the SS and LL options to the rat, followed by 20 free choice trials where the rat could select either option. Preliminary results show that rats' choices are sensitive to both reward size and delay. We developed a behavioral model that predicted trial-by-trial choice probabilities as the difference in subjective values of SS and LL options. We present preliminary results of fitting this model to rats' behavioral choices, and evaluating best-fit discounting parameters based on independent measures (e.g., hyperbolic fits to points of psychometric subjective equivalence). The task provides a powerful platform for relating the subjective value of discounted rewards to underlying neural mechanisms in future work.

Disclosures: A.C. Martin: None. **C.E.M. Golden:** None. **C.M. Constantinople:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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McKnight Scholars Award

Title: Role of OFC in state inference

Authors: *S. SCHIERECK[1], M. DEMAEGD[2], A. MAH[1], C. M. CONSTANTINOPLE[2];
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Abstract: Orbitofrontal cortex (OFC) has been implicated in myriad aspects of value-based decision making. However, the precise role of OFC in value-based decision making is still unknown. We trained rats on a temporal wagering task that requires rats to determine how long to wait for a water reward. The amount of time rats are willing to wait for each reward provides an explicit behavioral readout of rats' subjective value for the offered reward volume. Rewards are presented in blocks of trials with different reward distributions. Rats wait longer for the same reward when the opportunity cost, or the expected reward that is given up by continuing to wait, is lower ("low" reward blocks) compared to when it is higher ("high blocks"). Transitions between reward blocks are not cued, creating partially hidden states. Bilateral muscimol inactivation of lateral OFC (lOFC) reduced modulation of wait time by reward block. Rats adjusted their wait times after a block transition more slowly when lOFC was inactivated. Additional behavioral analyses and modeling revealed that, contrary to our prediction, rats did not revert to a model-free strategy to estimate the average reward when lOFC was inactivated.

To generate hypotheses about how lOFC contributes to behavior, we used a behavioral model that reproduces several aspects of rats' behavior, and includes interpretable parameters that map onto different aspects of the decision-making process. The model uses Bayes' Rule to predict the identity of the reward block and adjust wait times accordingly. We added a lapse rate to the model to control the probability of belief updating on the next trial. Increasing the lapse rate reproduced the behavioral effects seen with lOFC inactivation, including reduced sensitivity to the reward block and slower behavioral changes at the block transitions. These results suggest that OFC is important for updating subjective beliefs based on experience to infer the hidden state. We performed large-scale Neuropixels recordings from the lOFC of well-trained rats, as well as rats that experienced blocks for the first few training sessions. Interpretable dimensionality reduction methods (tensor decomposition) revealed that lOFC populations exhibit similar task-aligned activity in both groups of animals. We speculate that these dynamics reflect learned knowledge of within-trial task states. We present our ongoing analyses of neural dynamics in these groups, and our attempts to characterize neural signatures of belief updating in lOFC.

Disclosures: S. Schiereck: None. **M. DeMaegd:** None. **A. Mah:** None. **C.M. Constantinople:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR134.05/K12

Topic: H.03. Decision Making

Support: NIH Grant R01NS104834
NIH Grant R01MH134833
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Paul G. Allen Family Foundation

Title: Structure-function correlations among locus coeruleus norepinephrine neurons

Authors: *Z. SU[1], P. KOSILLO[2], K. JUNG[2], K. M. HAGIHARA[2], M. RUE[3], X. CHEN[1], B. R. LEE[4], E. C. HILTON-VANOSDALL[2], K. SVOBODA[2], J. V. CHANDRASHEKAR[2], J. Y. COHEN[2];
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Abstract: Norepinephrine (NE) is released through most of the central nervous system from the locus coeruleus (LC). LC-NE neurons modulate arousal, attention, and learning. This panoply of functions is often ascribed to broad projections across the brain. We reconstructed the morphologies of single LC-NE neurons and found that different LC-NE neurons projected to different regions in a non-overlapping manner. LC-NE neurons projected to cerebral cortex, or

cerebellum, or medulla and spinal cord. Anatomical tracing with RNA barcodes (BARseq) showed similar modules of LC-NE projection targets. We asked whether LC-NE neurons comprise distinct types of neurons with different functions during learning in mice. Electrophysiological recordings in brain slices revealed LC-NE cell types with two distinct shapes of action potentials: wide (type I) and narrow (type II). We made *in vivo* extracellular electrophysiological recordings and similarly found two clusters of action potential shapes among identified LC-NE neurons. To test whether these distinct types of LC-NE neurons had different functions, we measured neural action potentials from LC-NE neurons in a behavioral task requiring learning from reward prediction errors (RPE). Mice were trained to make choices to lick leftward or rightward for reward with changing probabilities. Because reward probabilities changed over time, they used reward and choice history to make future choices. Types I and II LC-NE neurons responded differently to decision outcomes. Type I neurons were excited by RPE while type II neurons were excited by lack of reward. Activity of the two types of neurons correlated with changes in future choices in opposite ways: higher activity in type I neurons predicted positive changes in policy updates (consistent with RPE), whereas higher activity in type II neurons predicted negative changes in policy updates. To determine how LC-NE dynamics correlates with projection targets, we performed two experiments. First, we used antidromic stimulation with collision tests to record electrophysiologically from LC-NE neurons with projections to cortex. Second, we measured axonal calcium dynamics (GCaMP) in LC-NE axons in frontal cortex, cerebellum, and medulla. LC-NE input to frontal cortex correlated with RPE. These results reveal a link between the structure and function of a major neuromodulatory system in the brain and show that NE provides a signal for cortex to learn from reinforcement.

Disclosures: Z. Su: None. **P. Kosillo:** None. **K. Jung:** None. **K.M. Hagihara:** None. **M. Rue:** None. **X. Chen:** None. **B.R. Lee:** None. **E.C. Hilton-VanOsdall:** None. **K. Svoboda:** None. **J.V. Chandrashekar:** None. **J.Y. Cohen:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.06/K13

Topic: H.03. Decision Making

Support: Paul G. Allen Funds
Simons Collaboration on the Global Brain Transition to Independence
Award (Poo: 863738)

Title: A novel olfactory patch foraging task to study decision making in head-fixed mice

Authors: *T. OÑA JODAR, B. CRUZ, T. RAMIREZ, O. UNOKESAN, K. NGUYEN, S. VASQUEZ, J. JUNG, N. MARS, A. CAHOON, C. POO;
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Abstract: Flexibility in an ever-changing world is key to survival and patch foraging decisions represent a natural example of this. Animals choose between exploiting local resources or leaving to explore potentially superior places (exploitation vs exploration).We developed an ethologically grounded olfactory patch foraging task to study flexible decision-making in head-fixed mice. Thirsty mice forage for clustered and depleting water reward patches on a closed-loop multi-sensory virtual track. Patches are defined by visual stimuli and reward sites within patches by olfactory cues (one type per patch). Naive mice acquire the task within 5 sessions. Mice make non-trivial patch leaving decisions that are sensitive to local and global reward statistics. We probed behavior under different reward depletion rules using distinct odor patches that share the same rate but with different initial values. When rewards deplete in size, individual mice maintained a constant reward size-leaving decision threshold across patch types (n= 9 mice). Surprisingly, a single leaving threshold was also observed when rewards depleted in probability (n = 12 mice), indicating that mice sample evidence from multiple harvests to guide their foraging choice. We show that the short acquisition time and minimal behavioral shaping allow mice to maintain behavioral flexibility and adopt distinct strategies as task parameters change within single sessions. Finally, we discuss our findings in comparison to predictions of an optimal forager by the Marginal Value Theorem. Future work will examine multi-regional neural dynamics underlying this behavior.

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Poster

PSTR134: Value-Based Decision Making in Rodents

Location: MCP Hall A

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Program #/Poster #: PSTR134.07/K14

Topic: H.03. Decision Making

Support: Allen Institute

Title: History-dependency in reinforcement learning tasks shapes dopamine dynamics on multiple timescales

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Abstract: The neurotransmitter dopamine (DA) is involved in various brain functions, including movement, motivation, and learning. Phasic DA activity, characterized by brief (hundreds of ms) bursts of dopamine release into the striatum, correlates with reward prediction errors (RPEs),

which represent the difference between predicted and actual outcomes and serve as a learning signal in reinforcement learning algorithms. However, many earlier studies used relatively simple Pavlovian conditioning paradigms involving passive exposure of reward-predicting stimuli and rewards. In contrast, recent work based on different behavioral paradigms suggests that DA may correlate more closely with a variety of context-dependent signals, including the value of the state, vigor, incentive salience, movement kinematics, causal associations, or learning rate. These contrasting findings underscore the need for a direct comparison of DA dynamics across different task paradigms.
To tackle this problem, we used fiber photometry and genetically encoded indicators to optically monitor DA release dynamics in the nucleus accumbens of head-fixed mice engaged in behavior. The mice participated in two distinct behavioral paradigms sequentially. The first paradigm, dynamic foraging, is an instrumental two-armed bandit task necessitating decision-making based on trial history. The second paradigm is a classical Pavlovian conditioning task, where three different conditioned stimuli (CSs) predict reward availability with varying probabilities. Notably, the two tasks differ in how they are learned: dynamic foraging involves ongoing, history-dependent decision-making process, whereas Pavlovian conditioning task involves expression of learned conditioned responses.
In the Pavlovian task, we found that phasic DA activity correlated well with RPEs at the time of outcomes, consistent with prior research. However, this correlation was not obvious in a dynamic foraging task, suggesting a task-dependent relationship between dopamine activity and reward prediction. Furthermore, tonic (1-10 s) dynamics tracked action value and reward history only in the foraging behavior. These findings provide a nuanced understanding of the role of DA in reinforcement learning, indicating that the relationship between DA activity and reward prediction may depend on the specific task and the timescale of DA activity (phasic vs tonic). Comparing DA release across tasks, may have implications for understanding the neural mechanisms underlying different types of learning and behavior.

Disclosures: K.M. Hagihara: None. **S. Recanatesi:** None. **H. Hou:** None. **K. Svoboda:** None. **J.Y. Cohen:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.08/K15

Topic: H.03. Decision Making

Support: NIH DP1 DA051608
NIH R01 DA051652

Title: Offline reactivation as a second window for value updates

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Abstract: One of the most important functions of the brain is selecting which action to perform. For instance, choosing the correct action can lead to successful hunting that allows survival. The process of decision-making is driven by values associated with actions, with high-value actions being selected over low-value ones. However, upon value changes, animals can quickly adapt and learn the new association. This updating process has been extensively studied but still not fully understood, with mechanistic theories still being proposed. Here, we investigate the update of values to actions through reactivation during offline periods. We trained mice to perform a two-alternative choice task with reward changing across trials. We recorded the activity of the Nucleus Accumbens and investigated its activity during hippocampal sharp-wave ripples in inter-trial intervals. We hypothesize that value-action association update is refined by reactivations of these associations during periods when mice are not performing the task.

Disclosures: E.F. Oliveira: None. **L.L. Sjulson:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Title: Contribution of value, risk and habit to behaviour and striatal activity of mice in probabilistic choice task

Authors: *Y. WANG[1], L. M. BURGENO[2], S. G. MANOHAR[3], M. E. WALTON[2], R. BOGACZ[4];
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Abstract: The basal ganglia (BG) are known to carry out critical functions in reinforcement learning and decision making. The direct and indirect pathways in BG characterised by striatal medium spiny neurons (MSNs) containing D1 and D2 dopamine (DA) receptors have opposite effects on their shared projection target. We designed a novel experiment to investigate whether the direct and indirect pathways together encode reward value and variability, and whether

different striatal areas are separately associated with value and habit driven behaviour. We devised a choice task in which mice learned to choose and sustain a response to the option with the highest probability of reward (4 μL water droplet) among three nose poke ports (positioned left, right and above of the initial holding position). The reward probabilities of the three options are 20%, 50% and 100%. Although the mapping of reward probabilities to port positions remained static within each session and across most consecutive sessions, it was also changed twice during the experiment, so the animals had to relearn the mapping after first achieving expertise. We recorded activity of MSNs in direct and indirect pathways as well as DA levels in both dorsolateral and dorsomedial striatum using fibre photometry while animals (n=40) performed the task. Mice became proficient at the task through learning, selecting the higher value option on choice trials between pairs of the ports and being more likely to sustain their response to higher value ports. However, they also displayed systematic biases towards particular options. We show through modelling that these biases could arise from a combination of value-independent habitual action selection and a preference for high outcome variance ("risky") actions. The commonly used trial-by-trial maximum likelihood fitting method gives an unreasonable advantage to the value-independent habit mechanism, undermining the effect of any other action selection mechanism within the same model. By employing a stochastic fitting method which computes latent variables through repeated simulations independent of the experimental data, we were able to achieve more effective model comparison and demonstrate that a combined model of value seeking, risk seeking and habitual actions is the best fitting to behavioural data among an array of candidates. Activity in direct and indirect pathway MSNs and DA levels were each shaped by the within-trial state (choice, hold, outcome delivery) and position and reward probability of selected port. DA levels further responded to reward outcome. Ongoing work will also include latent variables from fitted behavioural models in analysis of neural data.

Disclosures: Y. Wang: None. **L.M. Burgeno:** None. **S.G. Manohar:** None. **M.E. Walton:** None. **R. Bogacz:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.10/K17

Topic: H.03. Decision Making

Support: ANR

Title: How value representations are distributed along the primate basal ganglia circuits during decision-making?

Authors: *M. SIMIC, T. BORAUD, M. DEFFAINS;
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Abstract: Decision-making is a higher-order brain function that consists in choosing between behaviors/options. Basal ganglia (BG) dysfunction is known to be involved in decision-making deficits observed in patients suffering from BG-related disorders including neurological (e.g., Parkinson's disease) and psychiatric (e.g., obsessive compulsive disorders) disorders. However, the neural mechanisms and computations of decision-making in BG network are elusive and do not satisfactorily reflect the complex and known BG anatomy and physiology. Moreover, there are different types of value-related information (i.e., outcome value, action value, chosen value and choice only) the BG neurons encode which are required during value-based decision-making. To tackle these issues, we trained two rhesus monkeys in a task where they had to choose by performing arm reaching movements between two lotteries that probabilistically predicted different quantities of gains or losses of the same reward. Then, we performed multi-site and multi-electrode in vivo electrophysiological recordings (32 recording channels) within key ventral and dorsal areas of the BG network (i.e., ventral striatum and ventral pallidum vs. caudate nucleus and external globus pallidus) of the monkeys while they were engaged in the behavioral task. In doing so, we characterized distinct task-dependent activities related to the estimation and evaluation of the consequences/outcomes of the choices in the ventral areas and to the preparation and execution of these choices in the dorsal areas. This dichotomic function of the BG ventral and dorsal circuits is therefore likely to be critical to the implementation of BG physiology and pathophysiology.

Disclosures: M. Simic: None. **T. Boraud:** None. **M. Deffains:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.11/K18

Topic: H.03. Decision Making

Support: HHMI Hanna Gray Fellowship
NIH F32

Title: Interacting timescales of neural coding during sensory-driven behavior

Authors: *A. BOWEN[1], D. J. OTTENHEIMER[2], N. MACKENZIE[3], G. D. STUBER[5], N. A. STEINMETZ[4];
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Abstract: Adaptive behavior is multi-timescale, optimally integrating short and long-term information into a single decision process. We implemented a behavioral task in water-deprived headfixed mice to shape ingestive behavior over three distinct timescales: distinct sensory cues to instantaneously guide licking behavior, fluctuating probabilities of reward to modulate

anticipation across trials, and excess reward to progressively sate animals across the session. We recorded the spiking activity of ~16,000 neurons across cortex, striatum, amygdala, hypothalamus, thalamus, midbrain, pons, and medulla, and found that motor coding neurons across the brain exhibit slower intrinsic timescales than sensory coding neurons. To examine multi-trial coding properties, we developed a reinforcement learning model that revealed the synergistic impacts of recent reward history, overall reward rate, and satiety on individual subjects' behavior. Using the model value estimates to find value encoding neurons, we discovered ensembles carrying value information over distinct timescales, either scaling task sensory variables or tonically encoding trial value. Together, our data highlight the multi-timescale nature of neural computations and the interactions that occur to adaptively affect behavior.

Disclosures: A. Bowen: None. **D.J. Ottenheimer:** None. **G.D. Stuber:** None. **N.A. Steinmetz:** None.

Poster

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Program #/Poster #: PSTR134.12/K19

Topic: H.03. Decision Making

Support: IBS-R002-A1; M.W.J.

Title: Value-dependent activity of somatostatin- and VIP-expressing neurons in the rodent hippocampus

Authors: *J. JU[1,2], M. JUNG[1,2];
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Abstract: Although the hippocampus has traditionally been thought to represent primarily cognitive variables related to spatial navigation and episodic memory, a growing body of evidence indicates that it also represents value-related signals. To investigate the neural mechanisms underlying hippocampal value representation, we examined value-dependent discharges of inhibitory interneurons in dorsal CA1 in mice. Using one-photon calcium imaging, we recorded the activities of somatostatin (SST)- and VIP-expressing neurons in SST-Cre and VIP-Cre mice, respectively, during a probabilistic classical conditioning task. In this task, three different odor cues were associated with varying probabilities (75%, 25%, and 0%) of water delivery. We found that both SST and VIP neurons carry value-related signals, but with somewhat different characteristics. An analysis using GLM revealed that SST neurons convey value signals faster and stronger than VIP neurons upon cue presentation. SST neurons also conveyed stronger value and outcome signals than VIP neurons following outcome onset. During the outcome period, both SST and VIP neuronal responses were negatively related to reward but

positively related to value, suggesting their role in computing reward prediction error. These results suggest that both SST and VIP neurons contribute to hippocampal value representation, with SST neurons assuming a more prominent role. We are currently examining the activity of parvalbumin-expressing CA1 neurons within the same task framework. Additionally, we are investigating how modulating the activities of different interneuron subtypes impacts animal behavior and value-dependent activity of pyramidal neurons. These efforts have the potential to enhance our understanding of the neural underpinnings of hippocampal value representation.

Disclosures: J. Ju: None. **M. Jung:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.13/K20

Topic: H.03. Decision Making

Support: IBS-R002-A1; M.W.J.

Title: Value and spatial signal processing in the rodent granular retrosplenial cortex

Authors: *D. KONG[1,2], E. SHIN[1,2], M. W. JUNG[1,2];
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Abstract: The retrosplenial cortex (RSC) is intricately connected with diverse cortical and subcortical brain structures and is implicated in various cognitive functions such as spatial navigation, episodic memory, and value-based decision making. In rodents, the RSC comprises agranular and granular divisions, with the latter reciprocally connected with the hippocampus. In an effort to probe hippocampal-RSC interactions in value-based decision making, we examined the effects of inactivation and neural activity in the granular RSC (gRSC) in mice performing a dynamic foraging task in a figure 8-shaped maze. Bilateral inactivation of the gRSC using muscimol severely disrupted the animal's choice behavior in the task. Preliminary analysis employing reinforcement learning models suggests that gRSC inactivation increases choice bias while decreasing learning rate. Additionally, gRSC neurons recorded with one photon calcium imaging conveyed a diverse array of signals related to value-based decision making. Notably, they conveyed strong decision-value and chosen-value signals before and after the animal's selection of target, respectively, alongside encoding spatial information. A preliminary analysis indicated a positive relationship between decision-value signals and spatial information in neurons significantly responsive to decision value. These results suggest that the gRSC may conjunctively integrate value and spatial information to guide value-based decision making in freely navigating mice. Our future work aims to explore the underlying neural mechanisms by manipulating hippocampal inputs to the gRSC.

Disclosures: D. Kong: None. **E. Shin:** None. **M.W. Jung:** None.

Poster

PSTR134: Value-Based Decision Making in Rodents

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Program #/Poster #: PSTR134.14/K21

Topic: H.03. Decision Making

Support: Wellcome Trust
Royal Society
Human Frontier Science Program

Title: Distinct neuronal representations of economic variables across regions and projections of the frontal cortex

Authors: *A. MAJUMDAR, C. ASHCROFT, M. FRITSCHE, A. M. PACKER, S. BUTT, A. LAK;
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Abstract: We often make economic decisions in our daily lives which require us to evaluate and integrate different variables such as reward magnitude and risk to inform our choices. Previous studies have shown representations of such economic variables in distinct regions and projection pathways of the frontal cortex. However, these studies usually focused on select subpopulations of frontal cortical neurons. Therefore it remains unclear how representations of economic variables are structured within the frontal cortex and whether diverse frontal regions and their projections pathways encode distinct variables. To address this question we combined behavior, large-scale high-density electrophysiology and projection-specific optotagging to investigate how fine grained neural signals contribute to economic decisions. To this end, we devised a visual economic decision-making task in head-fixed mice, akin to those used in previous non-human primate studies. In each trial, mice chose between two simultaneously presented abstract visual stimuli that differed in their magnitude of associated water reward, and reward probability, resulting in options with different expected values and economic risks. Mice learned the task, consistently selecting stimuli with higher expected values. Population decoding of economic variables showed distinct gradients for different economic variables: expected value coding was stronger in dorsal compared to ventral frontal regions, while risk coding was stronger in medial compared to lateral regions. Moreover, by investigating a subset of neurons with optogenetically-identified projection pathways, we found that frontal neurons projecting to the claustrum encoded expected value while neurons projecting to the dorsomedial striatum more robustly encoded economic risk. This differential representation could not solely be explained by the spatial gradients we observed across frontal regions alone, because projection-defined cells were identified across all frontal cortical subregions. Our results shed light on the structure of the neuronal code underlying economic decision making, demonstrating that encoding of economic variables spans multiple scales of neural representation in the frontal cortex.

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Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.01/K22

Topic: H.05. Working Memory

Support: Center for Neuroinflammation and Cardiometabolic Diseases Seed Grant
Brains and Behavior Fellowship

Title: Uncovering the neurobiological role of endogenous fibroblast growth factor 21 as a high-fat diet-stimulated stress-response hormone

Authors: *H. LAIL[1], R. LAWRENCE[2], A. M. MABB[3], D. WANDERS[1];
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Abstract: Changes in the food environment have led to dramatic changes in people's diets, particularly in fat intake. These changes, along with the increased prevalence of diet-related diseases have prompted research into the physiological and cognitive implications of high fat consumption. FGF21 is an endogenous stress-response hormone elevated in response to HFD feeding. Administration of FGF21 improves both metabolic and cognitive health in preclinical models. However, the role of endogenous FGF21 in protecting the brain against HFD consumption remains unexplored. Moreover, there is evidence that suggests its function may differ by sex. Therefore, we aimed to identify whether endogenous FGF21 protects the brain from HFD-induced cognitive impairments in both sexes. Furthermore, we aimed to identify FGF21's mechanisms of protection by examining HFD-induced changes in the brain.
Male and female wild-type (WT) and FGF21 knockout (*Fgf21*$^{-/-}$) mice were fed a standard chow (13.6% fat) or HFD (60% fat) for 9 weeks (n = 7-8, diet x genotype x sex). Body weight was measured weekly. Serum FGF21 was measured by ELISA. Cognition was assessed by novel object recognition test, Barnes maze, and fear conditioning. Protein was isolated from whole brain and hippocampus and measured by western blot. Two-way ANOVA was conducted for all statistical analyses. A value of ($p < 0.05$) is considered statistically significant.
The HFD increased body weight in both sexes regardless of genotype ($p < 0.01$) and increased circulating FGF21 in WT mice ($p < 0.01$). In the novel object recognition test, the HFD impaired the recognition memory of WT mice regardless of sex ($p < 0.05$), while recognition memory was lost in *Fgf21*$^{-/-}$ mice independent of diet. In Barnes maze the HFD impaired spatial learning and memory of WT males, but improved female performance. The HFD did not impair the spatial cognition of *Fgf21*$^{-/-}$ mice. The HFD had no effect on associative learning and memory, assessed by fear conditioning, regardless of sex. Moreover, *Fgf21*$^{-/-}$ mice spent more time frozen overall ($p < 0.01$) compared to WT. In the brain, Sirtuin-1 (SIRT1) and NADPH oxidase isoform 2 (NOX2) were elevated by the HFD in WT males ($p < 0.05$), but not females. Whereas the HFD

increased ionized calcium binding adaptor molecule 1 (IBA1) in the hippocampus of WT males only.
Our data suggest that increased endogenous FGF21 in response to HFD intake does not protect against HFD-induced cognitive impairments or brain dysfunction. However, FGF21 may be essential for specific types of cognition, and a lack of FGF21 may be beneficial for protection from HFD-induced impairments in spatial cognition and associative learning and memory.

Disclosures: H. Lail: None. **R. Lawrence:** None. **A.M. Mabb:** None. **D. Wanders:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.02/K23

Topic: H.05. Working Memory

Title: Forebrain specific loss of erythropoietin provokes a compensatory upregulation of different EPO receptors

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Abstract: The procognitive growth factor erythropoietin (EPO) and its canonical receptor, EPOR, have long been recognized to be expressed by most cell types in the brain. Cognitive domains, improved by injections of exogenous EPO or by endogenous, hypoxia-stimulated EPO, include important forebrain functions, namely attention, working memory, drive, and executive performance. To gain mechanistic insight into the involvement of forebrain-expressed EPO, we deleted EPO in mice using the specific cre-driver *Emx1*. Here, we report the surprising observation, that these mutant mice act comparably to their wildtype littermates in a comprehensive behavioral test battery. Importantly, we find that the transcripts of both EPOR and a novel, brain-expressed EPO receptor, EphB4, respond to EPO deletion with compensatory upregulation. EphB4 expression in brain and its increase upon forebrain erasure of EPOR are confirmed by immunohistochemistry and *in situ* hybridization. The augmented expression of both EPOR and EphB4 may explain why *EmxEPO* mutants show an even superior performance

in the most challenging working memory task. Using our single-nuclei-RNA-seq dataset, we identify forebrain expression of *Emx* mainly in excitatory neurons with no alterations upon EPO. Collectively, these data explain the lack of behavioral and cognitive consequences on forebrain-wide elimination of EPO.

Disclosures: U. Butt: None. **A. Wildenburg:** None. **L. Ye:** None. **Y. Curto:** None. **A. Ronnenberg:** None. **V. Bonet:** None. **S. Boretius:** None. **K. Nave:** None. **H. Ehrenreich:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.03/K24

Topic: H.05. Working Memory

Title: Ficus infectoria ameliorates stress induced cognitive deficits by modulating BDNF and neuroinflammatory markers

Authors: *R. VASUDEV[1], *R. VASUDEV[1], T. KRISHNAMURTHY[1], B. BARAKA[2], V. BHAGYA[3];
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Abstract: Depression is a common disabling and life-threatening mental illness associated with significant morbidity and mortality. Chronic stress precipitates neuropsychiatric conditions and causes cognitive impairment, increases anxiety, and depressive-like symptoms. Prolonged stress disrupts brain derived neurotrophic factor (BDNF) and neuroinflammatory markers in the hippocampus and prefrontal cortex (PFC), with structural abnormalities.
Considering the increasing evidence regarding the importance of herbal drugs in treating neuropsychiatric disorders, the aim of this study was to investigate the effect of *Ficus infectoria* (FI) on chronic immobilization stress (CIS) induced cognitive deficits. Rats were subjected to CIS and then treated with the FI at two different doses for two weeks. Post treatment, the rats were subjected to behavioral analysis, biomarkers estimation and histopathological studies.
The rats exposed to immobilization stress showed impaired working memory and recognition memory in the T-maze and novel object recognition test, respectively. Stressed animals displayed increased anxiety-like behaviour in the open field and elevated plus maze, increased immobility time in the forced swim test and reduced sucrose preference. Additionally, stressed rats exhibited decreased BDNF and increased neuroinflammatory markers; tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), as well as atrophy within the hippocampus and PFC. Interestingly, *Ficus infectoria* administration alleviated impaired learning and working memory, anxiety, anhedonia, and immobility. FI significantly increased the BDNF levels and suppressed neuroinflammation in the hippocampus and PFC. In summary, the present study

highlights the neuroprotective effect of *Ficus infectoria* in CIS-induced cognitive deficits. Therefore, we propose that *Ficus infectoria* may be an effective natural compound in alleviating the negative effects caused by prolonged stress.

Disclosures: R. Vasudev: Other; KLE COLLEGE OF PHARMACY, KAHER, BENGALURU. **R. Vasudev:** Other; KLE COLLEGE OF PHARMACY, BENGALURU; KAHER. **T. Krishnamurthy:** None. **B. Baraka:** None. **V. Bhagya:** Other; KLE COLLEGE OF PHARMACY, BENGALURU; KAHER.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.04/K25

Topic: H.05. Working Memory

Support: Genomics and Translational Cancer Research Training Program (BIG-TCR) funded by the Cancer Prevention and Research Institute of Texas (CPRITCPRIT, RP210045) at The University of Texas Health Science Center at Houston.
UTHealth Programatic grant

Title: Longitudinal Analysis of Cognitive Dysfunction Induced by Whole Brain Radiation Therapy in Mice Model.

Authors: *M. BEKAL[1], Y. ESQUENAZI[2];
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Abstract: Radiation therapy is integral in treating brain tumors, yet its potential impact on cognitive function remains a concern. Understanding this relationship is vital for refining treatment approaches and improving patient outcomes. We explore the longitudinal effects of whole brain radiation therapy (WBRT) on cognition using a murine model, filling a gap in longitudinal research on cranially irradiated mice. In this study, Mice were irradiated with either 9Gy or 15Gy of radiation mimicking clinical scenarios, and their cognitive function was assessed using the Y-maze and Novel Object Recognition tests at 7, 30, 60, 90, and 150 days after irradiation. Our results show that mice irradiated with both 9Gy and 15Gy of radiation exhibited cognitive dysfunction compared to control mice in both the Y-maze and Novel Object Recognition tests, indicating deficits in spatial memory and recognition memory, respectively. These cognitive deficits were observed as early as 7 days after irradiation and persisted for up to 150 days post-irradiation. Interestingly, the severity of cognitive dysfunction was dose-dependent, with mice irradiated with 15Gy showing more pronounced deficits compared to those irradiated with 9Gy. Overall, our findings suggest that radiation therapy has long-lasting effects

on cognition in mice, underscoring the importance of the cognitive sequelae of radiation therapy and a dose-dependent relationship between radiation dosage and cognitive impairment. Moreover, our study fills this critical gap by employing a longitudinal approach to assess cognitive function at various time points following whole brain radiation therapy (WBRT) in mice. Our findings demonstrate that a single dose of cranial irradiation leads to long-term cognitive dysfunction, challenging previous assumptions regarding the potential reversibility of radiation-induced cognitive deficits. This unique aspect of our study underscores the novelty and importance of our murine model, which offers a valuable platform for future investigations into the long-term effects of radiation therapy.

Disclosures: M. Bekal: None. **Y. Esquenazi:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.05/K26

Topic: H.05. Working Memory

Title: Inactivation of hippocampal-frontal circuity during a touchscreen-based spatial working memory task

Authors: *F. L. D. L. ZAKAS[1], A. E. HARR[1], E. VOGT[1], N. A. FADIL[1], H. L. HALLOCK[2]; [2]Neurosci., [1]Lafayette Col., Easton, PA

Abstract: Tests of spatial working memory in rodents have typically relied on ambulation to a physical location on a maze in order to retrieve a reward. It is therefore the spatial location of the reward in Cartesian space that must be held in mind over the delay period. Studies have shown that the monosynaptic circuit between the ventral hippocampus and frontal cortex in rodents is critical for performance of these tasks. In contrast, human/primate spatial working memory tasks typically require the participant to keep the location of an item on a screen in mind over a temporal delay. These human/primate spatial working memory tasks do not typically engage the hippocampus, suggesting that the "spatial" aspect of the task determines which neural circuits support performance. To test the hypothesis that maintaining the spatial location of an object on a screen does not require hippocampal-frontal function, we trained male and female mice (n = 8-10 per group) on a touchscreen-based task of spatial working memory that has high face validity with human/primate tasks (TUNL). We injected viruses expressing inhibitory DREADD receptors selectively in hippocampal neurons with axonal projections to the frontal cortex (control mice received injections of a virus that does not contain the DREADD receptor). We then trained our mice to perform two versions of TUNL to proficiency. The first condition manipulates the physical separation between objects on the touchscreen, testing the mouse's ability to distinguish between the objects' position when they are physically closer to each other (S3 vs. S1). The second condition manipulates the temporal delay, testing the mouse's ability to distinguish between the objects' position when the amount of time between testing and choice

phases is increased (0 second vs. 4 second). We found that hippocampal-frontal circuit inactivation caused a decrease in choice accuracy when sample and choice objects were closer to each other on the touchscreen, but not when delay length was increased. These results are a first step toward demonstrating construct validity for the TUNL task, which is critically important for the assessment of preclinical utility of drugs for the treatment of disorders with spatial working memory deficits, such as schizophrenia.

Disclosures: F.L.D.L. Zakas: None. **A.E. Harr:** None. **E. Vogt:** None. **N.A. Fadil:** None. **H.L. Hallock:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.06/K27

Topic: H.05. Working Memory

Support: NIH Grant AOD24006-001-00000; MOA-AI-21002-01

Title: Exploring the effects of in utero acute organophosphorus nerve agent (OPNA) exposure on mouse behavior

Authors: *O. BELLEK[1,2], S. COE[1,3];
[1]USAMRICD, Edgewood, MD; [2]ORISE, Gunpowder, MD; [3]ORISE, Edgewood, MD

Abstract: Organophosphorus nerve agent (OPNA) poisoning leads to a cholinergic crisis resulting in difficulty breathing, seizures, and death due to the inhibition of acetylcholinesterase (AChE). Studying the effects of OPNA poisoning is difficult because common small animal research models produce serum carboxylesterase (CaE), an endogenous bioscavenger that offers protection against OPNA intoxication. Additionally, although AChE performs the same biochemical function in all animals, minor amino acid differences across species cause the enzyme to react quite differently to small molecules known as reactivators intended to restore the native activity of OPNA-inhibited enzyme. The KIKO (AChE Knock-In/CaE Knock-Out) mouse model incorporates two genetic modifications into a single animal that simultaneously addresses concerns for the chemical warfare agent research community and presents a unique opportunity for this animal to act as a model for the study of compounds which interact directly with AChE. This study aims to evaluate altered behaviors in offspring caused by an acute OPNA exposure *in utero.* The two main study objectives are: 1) explore the behavioral disturbances caused by *in utero* exposure to OPNA and/or countermeasures and 2) compare behavioral effects in C57BL/6J (WT) and KIKO mouse strains. In a previous study, pregnant mice were subjected to an acute OPNA exposure, and their offspring were analyzed for genetic abnormalities. While no changes in gross anatomy of the offspring were noted, several significant changes of gene expression profiles were found in exposed pups suggesting possible impacts on behavioral responses. The current study aims to quantify these potential changes via targeted behavioral testing in both WT

and KIKO strains. All mice will undergo behavioral testing at multiple time points throughout their life. Ages at evaluation may include sexually mature (6-8 weeks old), adult (14-16 weeks old), mid-life (40-42 weeks old), and geriatrics (78-80 weeks old). Elevated Zero Maze (EZM) and Morris Water Maze (MWM) will be used to evaluate anxiety and learning respectively. Behavioral disturbances may be carried into later generations and could be evaluated to determine this potential inheritance. The results from this study may provide insight to how OPNA or countermeasure could impact the offspring of exposed civilians and/or warfighters.

Disclosures: O. Bellek: None. **S. Coe:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.07/K28

Topic: H.05. Working Memory

Support: NIA Grant AG028084
NIH Alzheimer's Disease Core Center Grant P30AG019610
Arizona Department of Health Services Grant ADHS14-052688

Title: Testing a social recognition working memory load in the rat: task development and future directions for understanding menopause effects on cognition

Authors: *C. R. LIZIK[1,2], K. KELLEY-WOLFE[1,2], E. S. WU[1,2], S. ASADIFAR[1,2], J. L. VERPEUT[1,2], H. A. BIMONTE-NELSON[1,2];
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ

Abstract: In socially behaving animals, the ability to recognize members of one's species on an individual basis is a critical form of memory, mediating social interactions necessary for survival. Wild rodents demonstrate social recognition memory for members of their colony, which can contain hundreds of members, by abstaining from internal aggression and attacking unrelated intruders. In the laboratory, a variety of behavioral tasks quantify social recognition memory on the premise of novelty exploration, in which the time spent exploring a novel, never-met conspecific is greater than the time spent exploring a familiar, previously-met animal. These paradigms involve repeat exposure to the same individual and demonstrate a progressive decrease in exploration time as novelty is replaced by recognition. Other paradigms involve a binary choice between a novel or familiar conspecific. While these paradigms offer insight and value, they do not address the question of memory load, which increasingly taxes cognitive capacity as load increases. Here, we present a novel behavioral apparatus and protocol that we designed for the systematic evaluation of social memory with an increasing memory load in the rodent. We found that young, intact female rats could recognize numerous conspecifics simultaneously. Troubleshooting procedures and data from this task will be presented. This task provides a novel tool for the experimental evaluation of social memory across innumerable

neurobiological factors and related trajectories, including but not limited to age, hormonal manipulations, sex, and neurodegenerative disease.

Disclosures: C.R. Lizik: None. **K. Kelley-Wolfe:** None. **E.S. Wu:** None. **S. Asadifar:** None. **J.L. Verpeut:** None. **H.A. Bimonte-Nelson:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: H.05. Working Memory

Support: NIA Grant AG028084
NIH Alzheimer's Disease Core Center Grant P30AG019610
Arizona Department of Health Services Grant ADHS14-052688

Title: Hysterectomy-induced response to a pharmacological challenge on spatial working memory and retention in the rat

Authors: *M. W. OEVERMANN[1,2], C. R. LIZIK[1,2], E. S. WU[1,2], K. KELLEY-WOLFE[1,2], H. A. BIMONTE-NELSON[1,2];
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ

Abstract: Hysterectomy, the surgical removal of the uterus, is one of the most common gynecological procedures in individuals born with female reproductive organs. While not a heavily investigated domain of research, some work has shown that hysterectomy alone increases dementia risk in women, especially if it occurs at a younger age. Our laboratory developed a rodent model of hysterectomy to broaden the understanding of menopause variants that could impact cognition. Using this model, we have shown unique enduring spatial working memory detriments resulting from hysterectomy surgery alone on a water radial-arm maze task with an increasing working memory load. To further address the depth of hysterectomy-induced mnemonic challenges, the current study investigated the impact of a pharmacological challenge with the cholinergic antagonist scopolamine. Rats were randomly assigned to surgical treatment groups of Sham-controls or Hysterectomy. After surgery recovery, rats were trained on the delayed-match-to-sample (DMS) plus maze, which included an information and a series of retention trials, measuring spatial working memory and short-term retention. Next, rats were injected with scopolamine and given additional DMS testing. Hysterectomized rats made more errors after scopolamine as compared to non-hysterectomized rats. These results extend hysterectomy-induced cognitive findings to behavioral tasks that incorporate a cholinergic challenge.

Disclosures: M.W. Oevermann: None. **C.R. Lizik:** None. **E.S. Wu:** None. **K. Kelley-Wolfe:** None. **H.A. Bimonte-Nelson:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.09/K30

Topic: H.05. Working Memory

Title: Dose-dependent shifts in spatial working memory and hippocampal adiponectin receptor expression with 17beta-estradiol treatment in young-adult ovariectomized rats

Authors: L. LEMAJEUR, **Y. ZAIOOR**, N. PATEL, S. KUJAWA, *A. PRAKAPENKA; Midwestern Univ., Downers Grove, IL

Abstract: Across a female's reproductive lifespan, estrogens are neuroprotective and cognitively beneficial. In parallel, estrogen deficiency, such as with menopause, increases risk for neurodegeneration and can worsen cognition. Hormone therapy that contains 17β-estradiol (E2) improves undesired symptoms linked to declines in estrogen. However, when evaluated for cognitive effects, E2 can improve, impair, or have no effects depending on E2 dose or the task at hand. Notably, E2 can also shift a female's metabolic profile, with changes in energy expenditure, body weight, and adipose tissue, which corresponds to altered adiponectin levels. In the hippocampus, adiponectin receptors AdiopR1 and AdipoR2 were shown to increase neurogenesis and synaptic plasticity, respectively. Therefore, it is plausible that E2 effects on learning and memory are mediated not only by the hormone's dose and task at hand, but also by metabolic status. We hypothesize that in a rat model of estrogen deficiency, E2 modulates spatial working memory in a dose-dependent manner, corresponding to food-restriction status and hippocampal adiponectin receptor expression. In our model, Sprague-Dawley rats (3-5-months-old) were ovariectomized and two weeks later (1) placed on a one-week food-restriction regimen and tested on the spontaneous alternation (SA) or delayed SA (dSA) tasks, (2) free-fed and tested on the dSA task, or (3) kept behaviorally naïve for either feeding condition. For two days prior to behavior or tissue collection, rats were randomly assigned to subcutaneous injections of vehicle (sesame oil), low E2 (0.01 µg/day), medium E2 (3 µg/day), or high E2 (10µg/day). High E2 impaired SA behavior in food-restricted rats on the SA task compared to vehicle, low E2, and medium E2, suggesting impaired spatial working memory with high E2; there were no effects of treatment on the more taxing dSA task. Although E2 dose did not impact adiponectin and AdipoR1 hippocampal gene expression, high E2 decreased AdipoR2 expression in relation to the vehicle. In free-fed rats, SA behavior exhibited a U-shaped dose-dependent effect of E2 on the dSA task such that the medium E2 treatment resulted in greatest spatial working memory impairment. Ongoing work is examining adiponectin, AdipoR1, and AdipoR2 hippocampal gene expression in behaviorally naïve free-fed rats and navigational strategies used on the SA and dSA tasks across E2 dose. Altogether, our findings indicate an inverse relationship between E2 and hippocampal AdipoR2 gene expression in food-restricted females, which corresponds to the impairing effects of E2 on spatial working memory in the context of menopause-associated estrogen deficiency.

Disclosures: L. Lemajeur: None. **Y. Zaioor:** None. **N. Patel:** None. **S. Kujawa:** None. **A. Prakapenka:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.10/K31

Topic: H.05. Working Memory

Title: Tracking developmental changes in spatial orientation using organization of open field behavior in the 5xFAD mice model.

Authors: *L. ROBLIN[1], C. SAN MARTIN URBINA[1], I. MURILLO[1], R. I. LAKE[1], H. SAMPSON[1], M. L. HASTINGS[2], D. G. WALLACE[3];
[1]Northern Illinois Univ., DeKalb, IL; [2]Pharmacol., Univ. of Michigan, Med. Ctr., Ann Arbor, MI; [3]Psychology, Northern Illinois Univ., DeKalb, IL

Abstract: Wandering behavior or becoming lost in familiar environment is frequently observed during the progression of Alzheimer's Disease (AD) and can be extremely dangerous. The accumulation of amyloid-beta peptide has been implicated in the neuropathology and cognitive deficits associated with AD. This study investigated changes in spatial orientation in a 5xFAD mouse model of AD that is associated with development of severe amyloid pathology. Movement was recorded under dark and light conditions as each mouse was placed on a round table with a small plastic tab attached to the edge. Noldus (video tracking software) was used to digitize the position of the mouse on the open field during the 20-minute session. This data was collected longitudinally when the mice were three, six, nine, and twelve months old. The resulting x- y-coordinates were segmented into stops and progressions. Significant group differences were observed in the topographic and kinematic characteristics of open field organization. These observations are consistent with impaired spatial orientation in the 5xFAD mice. This study furthers the understanding of impaired behavior in individuals suffering from AD. The persistence of the disruption in the organization of open field behavior observed in the 5xFAD mouse model establishes a foundation to evaluate the long-term efficacy of novel therapeutic interventions.

Disclosures: L. Roblin: None. **C. San Martin Urbina:** None. **I. Murillo:** None. **R.I. Lake:** None. **H. Sampson:** None. **M.L. Hastings:** None. **D.G. Wallace:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.11/K32

Topic: H.05. Working Memory

Title: Untangling Alzheimer's disease: String-pulling task reveals fine motor control deficits in the 5xFAD mouse model

Authors: *H. SAMPSON[1], A. GONZALEZ[2], R. I. LAKE[1], M. L. HASTINGS[3], D. G. WALLACE[2];
[1]Northern Illinois Univ., DeKalb, IL; [2]Psychology, Northern Illinois Univ., DeKalb, IL; [3]Dept. of Pharmacol., Michigan Med., Univ. of Michigan, Ann Arbor, IL

Abstract: Alzheimer’s disease (AD) patients exhibit deficits in motor function that interfere with daily activities. Locomotor deficits have been identified in the 5xFAD mouse model; however, work has yet to characterize fine motor deficits in this model. The 5xFAD model mimics amyloid plaque accumulation which may impact neural systems involved in fine motor control such as the sensorimotor cortex. Devascularization of the sensorimotor cortex has been observed to disrupt the string-pulling behavior. The current experiment investigated differences in string-pulling behavior between nine-month-old control (n=10) and 5xFAD (n=12) mice. String-pulling behavior was recorded for three trials with one-meter string. Disruptions in string-pulling behavior was observed in the 5xFAD mice at nine months of age. These results are consistent with amyloid pathology at this age disrupting fine motor control and establishes string-pulling behavior as an assessment for novel therapeutic interventions for AD.

Disclosures: H. Sampson: None. **A. gonzalez:** None. **R.I. Lake:** None. **M.L. Hastings:** None. **D.G. Wallace:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.12/K33

Topic: H.05. Working Memory

Title: Developmental change in human fine motor during the string-pulling task

Authors: Z. PROPER, A. LAROUECH, H. SAMPSON, R. LAKE, A. GLADFELTER, ***D. WALLACE**;
Northern Illinois Univ., DeKalb, IL

Abstract: The string-pulling task spontaneously elicits behavior that depends on fine motor control and is coordinated bimanually. Acquired and genetic mouse models of neurological conditions have been observed to disrupt the organization of string-pulling behavior; however, it remains to be determined the neurotypical sequence of development associated with this behavior. The current study used a cross-sectional design to examine age-related changes in the

topographic and kinematic characteristics of string-pulling behavior. Human participants aged five to nine years were recorded at 240 frames per second while engaged in string-pulling behavior. DeepLabCut was used to track hand position during bouts of continuous string-pulling behavior, and movements were segmented into reach and withdraw phases. A significant direct relationship was observed between age and reach heading consistency. String-pulling behavior relies on the development of neural systems involved in fine motor control. These results establish a foundation to evaluate translational models of developmental disability in fine motor control.

Disclosures: Z. Proper: None. **A. LaRouech:** None. **H. Sampson:** None. **R. Lake:** None. **A. Gladfelter:** None. **D. Wallace:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Topic: H.05. Working Memory

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SNSF grant 310030_215572 to A.C.
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Title: The claustrum stores information used for working memory

Authors: *A. BHATTACHARJEE[1], C. HUBER[1,2], B. UNSAL[1,2], J.-R. RENFER[1,2], I. RODRIGUEZ[3], A. CARLETON[1];
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Abstract: Working memory (WM), a pivotal cognitive mechanism, empowers the brain to transiently hold and manipulate information, enabling us to perform complex mental functions, including learning, decision-making, and communication. It has been classically envisioned as a process involving a distributed network across the brain's cortical and subcortical regions. A prevailing hypothesis in the field suggests the intriguing possibility of generalized memory storage within this network, a concept awaiting empirical substantiation. Such a store would presumably require an extensive network of bidirectional connections to the various cortical areas, given the heterogeneous nature of the data processed by WM. The claustrum (CLA), notable for its extensive reciprocal connectivity with neocortical regions, is well-positioned to be a key player in WM. To investigate its role, we recorded neuronal activity in the CLA of mice during engagement in olfactory and tactospatial delayed non-match to sample WM tasks. Our observations revealed neurons that were selectively responsive to stimulus cues, and delay-

specific cells, that maintained activity well beyond the stimulus presentation, suggesting a role in sustaining WM. We also observed that activity within CLA neuronal populations allowed for the decoding of cue identity after the stimulus had ended, though this ability waned as time progressed. This decline is reminiscent of the behavior seen in mice, indicating a potential parallel between CLA activity and WM capability. Strikingly, when we applied targeted chemogenetic inhibition to these CLA neurons, we observed a consequential impairment in WM. This decline was not limited to a specific type of information but spanned the different categories of information. This result underscores the CLA's central importance, possibly acting as a dynamic hub for transient information storage within the WM circuitry. The implications of our findings extend beyond the architectural mapping of WM. They offer fresh perspectives on the CLA's function, challenging existing paradigms and suggesting a more versatile role for the claustrum in cognitive processing. Our work opens new avenues for understanding the underlying mechanisms of WM and holds potential for developing interventions targeting cognitive dysfunctions where WM is disrupted.

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Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.14/L1

Topic: H.05. Working Memory

Support: ERC StG MEMCIRCUIT 758032

Title: Distinct behavioral and neuronal signatures of delayed response and working memory tasks in freely moving mice

Authors: *V. HOHENDORF[1,2], S. N. JACOB[1];
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Abstract: Short-term storage of sensory information in working memory (WM) is an important function of the prefrontal cortex (PFC) and the foundation of intelligent behavior. Working memory tasks differ from delayed response (DR) tasks, in which sensory information does not need to be maintained online for manipulation and instead the motor output can be readily planned. We therefore hypothesized that in WM, but not DR tasks, memory traces of the to-be-remembered sample would be actively maintained throughout the delay, whereas in DR information about the animals' upcoming choice would dominate. To investigate this hypothesis, we trained freely moving mice (n = 15) on a touchscreen-based spatial non-match-to-location task. Importantly, training proceeded in two steps. We first trained on a DR task, in which the

animals could use the sample stimulus location to fully predict the location of the correct test stimulus. We then trained on a WM task, in which the animals had to memorize the sample location without being able to predict the test location and prepare an action. Mice met criterion performance in both task types but showed faster learning and higher performance in DR compared to WM conditions. Locomotion analysis showed that the animals displayed idiosyncratic strategies to meet the tasks' different behavioral demands, which had to be adapted when progressing from DR to WM. During expert sessions of the respective tasks, we imaged medial PFC pyramidal neurons expressing GCaMP6f using single-photon head-mounted miniature microscopes (n = 1319 neurons from 6 mice). We found individual neurons significantly tuned to sample location, choice and trial outcome, exhibiting monotonic and labelled line tuning patterns. Importantly, during the sensory epoch the fraction of sample-selective units increased earlier and more strongly in the WM task than in the DR task (25% and 14% at peak, respectively) and remained higher throughout the delay epoch (17% and 8%, respectively). This pattern was reflected in the strength of sample coding in single neurons. Sample location during the sensory epoch and choice location during the test epoch were encoded by sparse, non-overlapping populations with only few mixed-selectivity units. These populations were anatomically homogeneously distributed rather than clustered. In summary, we find evidence for distinct behavioral and neuronal signatures associated with delayed response and working memory tasks, illuminating a crucial difference in their respective cognitive requirements.

Disclosures: V. Hohendorf: None. **S.N. Jacob:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.15/L2

Topic: H.05. Working Memory

Support: SNSF GRANT 32003B_200763

Title: The effect of fampridine on working memory: A randomized controlled trial based on a genome-guided repurposing approach

Authors: A. PAPASSOTIROPOULOS[1], V. FREYTAG[2], ***N. SCHICKTANZ**[3], C. GERHARDS[1], A. AERNI[1], T. FALUDI[1], A. HARINGS-KAIM[1], E. AMINI[1], E. MÜGGLER[1], T. SCHLITT[1], D. J. DE QUERVAIN[1];
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Abstract: Working memory (WM), a key component of cognitive functions, is often impaired in psychiatric disorders. Through a genome-guided drug repurposing approach, we identified

fampridine, a potassium channel blocker used to improve gait in multiple sclerosis, as a candidate for modulating WM. In a subsequent double-blind, crossover, randomized, placebo-controlled trial in 43 healthy young adults (ClinicalTrials.gov, NCT04652557), we assessed fampridine's impact on WM (3-back d-prime, primary outcome) after repeated administration. Independently of baseline cognitive performance, no significant main effect was observed (Wilcoxon P=0.87, r=0.026). Lower baseline performance was associated with higher working memory performance after repeated intake of fampridine compared to placebo (ρ=-0.37, P=0.014, n=43). In participants with low baseline performance, fampridine improved working memory compared to placebo (r=0.54, P=0.035, n=15). Additionally, repeated intake of fampridine lowered resting motor threshold ($F_{(1,37)}$=5.31, P=0.027, $R^2\beta$=0.01), the non-behavioral secondary outcome, indicating increased cortical excitability linked to cognitive function. Fampridine's capacity to enhance WM in low-performing individuals and to increase brain excitability points to its potential value for treating WM deficits in psychiatric disorders.

Disclosures: A. Papassotiropoulos: 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.; Swiss National Science Foundation, co-founder of GeneGuide AG. **V. Freytag:** None. **N. Schicktanz:** None. **C. Gerhards:** None. **A. Aerni:** None. **T. Faludi:** None. **A. Harings-Kaim:** None. **E. amini:** None. **E. Müggler:** None. **T. Schlitt:** None. **D.J. De Quervain:** 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.; Swiss National Science Foundation, co-founder of GeneGuide AG.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.16/L3

Topic: H.05. Working Memory

Support: NIMH Grant R01MH122613

Title: Working memory constructs joint probabilistic task representations for decision-making

Authors: *X. CHEN[1,2], J. JIANG[3], K. HWANG[3];
[1]The Univ. of Iowa, Iowa City, IA; [2]Psychological and Brain Sciences, University of Iowa, Iowa City, IA; [3]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: The human brain has a remarkable ability in extracting and integrating relevant data for guiding actions and decisions. This capacity in part depends on working memory, which maintains and manipulates task-relevant information in the service of goal-directed behavior. Theories and experimental evidence suggest that the mnemonic mechanisms of working memory

functions probabilistically, implying its potential to form a joint distribution for integrating multiple working memory representations. Yet, it remains an open question whether this operation incorporates uncertainty of maintained content when constructing task representation for guiding decisions, especially in the presence of multiple working memory inputs. Our study investigates whether working memory integrates multifaceted information probabilistically or deterministically. We designed a behavioral task requiring subjects to make decisions based on multi-dimensional working memory content, with four levels of ambiguity associated with each dimension of working memory features. We observed that both response time ($F(6,120)=9.20$, $p<0.0001$) and error rates ($F(6,120)=50.85$, $p<0.0001$) increase with the cumulative ambiguity of working memory representations. Through computational modeling, we found that a probabilistic model, which integrates working memory uncertainty, outperformed deterministic models. Protected exceedance probability analysis strongly favored the probabilistic model (protected exceedance probability=0.9996, Bayes Omnibus risk= 1.9853e-05). This suggests that working memory likely employs an operation that incorporates information uncertainty to integrate multiple representations, thereby guiding decision-making.

Disclosures: X. Chen: None. **J. Jiang:** None. **K. Hwang:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.17/L4

Topic: H.05. Working Memory

Support: Canada Research Chair Dynamics of Cognition FD507106 (RBE)
NSERC Discovery Grant RGPIN-2020-05577 (RBE)

Title: Value modulates memory-guided saccades

Authors: *M. ABBASZADEH[1], E. OZANICK[3], B. A. EBITZ[2];
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Abstract: Saccadic eye movements to high-value targets tend to be faster and more vigorous than saccades to low-value targets. However, it is not clear whether the same is true for planned eye movements: saccades made in the absence of a high-value visual stimulus. To determine if planned eye movements are also affected by target value, we manipulated value in a memory-guided saccade task in humans and a rhesus monkey. In this task, participants were required to memorize the location of a high- or low-value object, randomly presented among eight locations around an imaginary circle. Following a delay period, and upon receiving a go cue, participants executed a saccade to the remembered location in each trial. Participants had no prior exposure to the objects, value was randomly assigned to the objects, and knowledge about object value was acquired via repeated exposure during the task. To determine when participants learned the

value of the objects, we incorporated probe trials where both high and low-value objects were presented in opposing locations, requiring the participants to select between them. Initially, upon the first exposure to the objects, there was no significant difference between saccades to high- and low-value objects. However, with increasing exposure, we observed a notable enhancement in the speed, accuracy, and precision of saccades directed towards locations of high-value objects compared to those of low-value objects. At the same time, participants developed a preference for high-value targets in the probe trials. Additionally, saccades towards high-value object locations tended to be hypermetric and saccades towards low-value object locations were more hypometric. These findings suggest that planned eye movements are impacted by the value of a remembered object, despite the fact that the object is no longer on the screen. Neural recordings in the frontal eye fields (FEF) will determine how object value affects the neural signatures of planned eye movements.
Keywords: Saccadic eye movements, Memory-guided saccade, Value perception, Oculomotor control, Cognitive flexibility

Disclosures: M. Abbaszadeh: None. **E. Ozanick:** None. **B.A. Ebitz:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.18/Web Only

Topic: H.05. Working Memory

Title: Independence of kinesthetic working memory from auditory verbal working memory

Authors: *H. WEI[1], Q. ZHANG[1], G. SU[1], J. LIU[1], Y. QIU[2];
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[2]Beijing Fengtai Rehabil. Hosp., Beijing, China

Abstract: Kinesthetic and visual-verbal working memories are distinct subcomponents of working memory. We devised two types of verbal working-memory tasks, one visual and one auditory. The independence of kinesthetic working memory from auditory-verbal working memory has not yet been examined. To investigate the independence of kinesthetic working memory from auditory-verbal working memory using a dual-task method in terms of double dissociation. Twenty-two young adults (11 female, 11 male; mean age ±SD of 26 ±5 y) participated in this study. The three working memory tasks mentioned above were completed first without and then with the two secondary interference tasks. Secondary tasks included verbal and movement tasks. The order of the working memory and secondary interference tasks was counterbalanced across the participants using a Latinsquare design. The scores and spans of the tasks for kinesthetic working memory with a secondary movement task were significantly lower than those for a secondary verbal task ($P < 0.05$). The scores and spans of the auditory verbal working-memory tasks with a secondary verbal task were significantly lower than those with a secondary movement task ($P < 0.05$). The scores and spans of the visual verbal working-memory

tasks with a secondary verbal task were significantly lower than those with a secondary movement task ($P < 0.05$). These results suggest that kinesthetic and auditory-verbal working memories have distinct subcomponents. The working memory model includes the components of kinesthetic movement.

Disclosures: H. Wei: None. **Q. Zhang:** None. **G. Su:** None. **J. Liu:** None. **Y. Qiu:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.19/L5

Topic: H.05. Working Memory

Title: Deficit in working memory associates with increased tactile funneling illusion and schizotypy scores

Authors: *F. M. KASSIM[1], M. ALBRECHT[2];
[1]Biomed. and Clin. Studies, Linkoping Univ., Linkoping, Sweden; [2]Univ. of Western Australia, Perth, Australia

Abstract: Background: People with schizophrenia or those high in schizotypy have been found to exhibit deficits in working memory (WM) and widened stimulus binding windows (BWs) during illusory perception tests. Current models of WM propose an episodic buffer compartment of WM where integration of multiple and multimodal stimuli occurs, suggesting that the binding of stimuli into a percept of a single event or object is an integral function of episodic WM. The present study aimed to examine the associations of spatial SWM (SWM) and verbal WM (VWM), overall schizotypy score, and tactile funneling illusion (TFI) in healthy participants. **Methods:** In this study, a total of 68 healthy young participants were recruited, with 64 of them completing all three measurements in three consecutive studies. Spatial span and digit span were utilized to assess SWM and VWM, while tactile illusion was measured using the TFI test at various temporal (0, 500, and 750 ms) and spatial (5, 4, 3, 2, and 1 cm) intervals. The illusory measures were funneling and errors of localization (EL). To assess schizotypy, five psychometric rating scales were administered. **Result:** The findings showed that that there were significant negative associations between schizotypy score and WM (overall WM: $\rho = -0.28$, $p = 0.02$, $n = 64$; **VWM:** $\rho = -0.26$, $p = 0.04$, $n = 64$), but not for SWM ($\rho = -0.19$, $p = 0.13$, $n = 64$). No associations were found between schizotypy scores and TFI (funneling illusion: $\rho = -0.03$, $p = 0.20$, $n = 64$; EL: $\rho = -0.13$, $p = 0.50$, $n = 64$). However, negative associations were observed between WM and funneling illusion (overall WM: $r = -0.31$, $p = 0.01$; **SWM:** $r = -0.34$, $p = 0.007$; VWM: $r = -0.21$, $p = 0.09$). There were no significant associations between WM and EL (overall WM: $r = -0.11$, $p = 0.37$; SWM: $r = -0.16$, $p = 0.19$; VWM: $r = -0.05$, $p = 0.69$). **Conclusion:** The results indicate that the negative associations of WM and funneling illusions are possible without the influence of schizotypy, and that degree of schizotypy might not predict the level of funneling illusion in the general young population. Furthermore, the results showed

that SWM and VWM components of WM could be associated with separate entities. Overall, the association between WM and funneling illusion could relate to a new emerging concept “Tactile Working Memory.”

Disclosures: F.M. Kassim: None. **M. Albrecht:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.20/L6

Topic: H.05. Working Memory

Title: Working memory, speed and efficiency in reading comprehension in university students

Authors: *D. BOLANOS-RAMÍREZ, E. R. VILLUENDAS-GONZALEZ;
Psychology, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico

Abstract: Reading comprehension is a multifaceted process influenced by various cognitive functions such as language skills, memory, and attention. It not only requires decoding written words but also relies on prior knowledge and reading proficiency, influenced by factors like working memory capacity and reading speed. Working memory, a cognitive function involving temporary storage and manipulation of information, plays a crucial role in tasks like language comprehension, learning, and reasoning, enabling internal representations to guide decision-making and behavior. Numerous studies have highlighted the significance of reading abilities in academic performance across all levels. AIM: This study aimed to explore the relationship between working memory, orthographic knowledge, reading speed, and comprehension among university students. METHODS: The researchers utilized an electronic version of the Sternberg task, employing loads of 3, 5, and 7 elements, to measure working memory. Additionally, they employed an adult spelling knowledge battery comprising various subtests (e.g., homophone spelling choice, dictation, error detection in a text, and free writing) to assess reading skills. Fifteen college students from a Mexican university participated in the study, consisting of 13 females and 2 males, including 7 seniors and 8 freshmen. RESULTS: The researchers employed a multiple regression model, using a backward method, to predict reading comprehension. Predictors included orthographic error detection, working memory, errors in dictation and free writing, and writing speed, with homophone error detection excluded due to negligible contribution. The model demonstrated a satisfactory fit, explaining approximately 80% of the variation in reading comprehension ($F(6,8)=5.02$, $p<.05$, $R^2=.79$). These findings suggest that orthographic knowledge, reading speed, and working memory performance can serve as predictors of students' reading performance during their undergraduate studies. However, further research is warranted to elucidate whether enhancements in these abilities positively impact reading comprehension.

Disclosures: D. Bolanos-Ramírez: None. **E.R. Villuendas-Gonzalez:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.21/L7

Topic: H.05. Working Memory

Support: NIH Grant R01 NS132926

Title: Parallels between motor working memory and motor learning

Authors: *H. HILLMAN[1,2], A. D. FORRENCE[3], S. D. MCDOUGLE[1,2];
[1]Psychology, Yale Univ., New Haven, CT; [2]Wu Tsai Institute, Yale University, New Haven, CT;
[3]Wu Tsai Inst., Yale Univ., New Haven, CT

Abstract: Movements can be remembered over short timescales (e.g., via "motor working memory", MWM) and adapted over long timescales (e.g., via visuomotor adaptation). In this study, we investigate whether one's ability to retain certain types of movement information in MWM correlates with their ability to adapt movements in response to visuomotor prediction errors. Specifically, we examined how effector-specific (proprioceptive) and effector-independent (abstract) MWM codes might correlate with implicit and explicit components of visuomotor learning. To do so, participants completed a non-visual MWM task in which they switched hands in half of the trials between encoding and recalling a passive reaching movement. Our previous work demonstrated that this task effectively separates effector-specific and effector-independent aspects of MWM, as participants cannot rely on effector-specific cues when recalling movements with the opposite arm. The same participants then completed a standard visuomotor rotation adaptation experiment designed to measure both implicit and explicit contributions to motor adaptation. Our key results were twofold: We found a significant correlation between the precision of effector-specific MWM and implicit motor learning, suggesting that short-term somatosensory representations are likely involved in implicit motor adaptation. Similarly, we found a significant correlation between effector-independent MWM and explicit motor learning, indicating the recruitment of shared abstract spatial reasoning resources across both tasks. Control analyses ruled out general effects of effort that may have confounded the observed cross-task correlations. Taken together, these results shed light on the complicated relationship between motor working memory and motor learning, demonstrating how the precision of short-term motor representations - both sensory and abstract - may influence error-based motor learning.

Disclosures: H. Hillman: None. **A.D. Forrence:** None. **S.D. McDougle:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.22/L8

Topic: H.05. Working Memory

Support: NSF BCS-1921415 to SS
BCS-2022572 to DJK and SS

Title: The strength of visual working memory representation deteriorates with age

Authors: *S. TKACZ-DOMB[1], S. SHOMSTEIN[1], D. J. KRAVITZ[1,2];
[1]The George Washington Univ., Washington, DC; [2]Natl. Sci. Fndn., Alexandria, VA

Abstract: Previous studies show bidirectional interference between visual working memory (VWM) and ongoing perception, consistent with the common recruitment of perceptual cortical areas (e.g., Teng & Kravitz, 2019) in tasks requiring the maintenance of visual detail. Here, we hypothesized that the strength of the maintained representation in perceptual areas will degrade with age. In three experiments, participants titrated by decade (ages 20 to 69), were asked to maintain a memory cue (color, orientation, face identity) while performing a detection task in which a sequence of letters appeared on a task-irrelevant background matching the maintained feature. Following a white letter detection task, participants reported the maintained memory cue using a continuous report. Similarity between the maintained memory cue and the task-irrelevant background was manipulated. For each similarity condition, we measured the bias of the response from the memory cue towards the task-irrelevant background and the standard deviation of the error distribution that conveys the quality of the representation. In all experiments perceived information altered information in visual working memory, such that as the similarity between the memory cue and the distractor background increased, so did the bias and standard deviation. Additionally, with both, we found a greater amplitude of bias toward the task-irrelevant background and a larger standard deviation with increasing age. Together, these findings identify a very specific way in which VWM degrades with age, pointing to a decrease in the fidelity of memory representations.

Disclosures: S. Tkacz-Domb: None. **S. Shomstein:** None. **D.J. Kravitz:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.23/L9

Topic: H.05. Working Memory

Support: Operation Mend

Title: Prospective memory concerns in treatment-seeking veterans: correlation with cognitive measures.

Authors: D. STALEY[1], S. KUNRATH[1], E. THRASHER[1], *B. J. KNOWLTON[2];
[1]UCLA, Los Angeles, CA; [2]Psychology, UCLA, Los Angeles, CA

Abstract: Previous research on treatment-seeking veterans with a history of TBI and/or PTSD has shown large self-reported prospective memory (PM) deficits when compared to age, gender, and education matched controls. These PM deficits are important to track and address as difficulty with prospective memory has shown to be a key predictor of difficulty in daily life. However, the cognitive processes behind these prospective memory deficits are not fully elucidated. Successful PM performance is a complicated process that relies on both working and retrospective memory. In order to create an effective intervention for PM deficits it is important to determine the memory process that is being most affected.Data was available from 81 treatment-seeking veterans during their diagnostics at Operation Mend. Veterans completed the PM concerns questionnaire (PMCQ) as a measure of prospective memory concerns and were assessed on their working and retrospective memory with the WAIS-4 digit span task and the California Verbal Learning Test (CVLT), respectively.A multiple linear regression was conducted in which age, gender, CVLT Long Delay Free recall, and Digit Span Total Score were used to predict scores on the PMCQ. The slope of the CVLT subscore was not statistically significant indicating that retrospective memory performance is not having a significant effect on self-reported PM failures and concerns. However, the slope of Digit Span Total Score was statistically significant($t(75)= -2.446$, $p = .017$, 95% CI = [-1.629, -.166]. After removing the variability from digit span total score that can be explained by age, gender, and CVLT Long Delay Free recall scores via a semi-partial correlation, the correlation between digit span and PMCQ scores is -0.268. This indicates that better performance on the digit span task was correlated with less self-reported PM concerns and failures.The results from this study suggest that the PM deficits this population experiences are more closely associated with working memory than retrospective memory. This suggests a possible difficulty maintaining PM intentions in their working memory throughout the retention period of their regular PM tasks. Future interventions should incorporate strategies to address working memory deficits in order to improve real-life prospective memory performance.

Disclosures: D. Staley: None. **S. Kunrath:** None. **E. Thrasher:** None. **B.J. Knowlton:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.24/L10

Topic: H.05. Working Memory

Support: NIH Grant R15MH122935 to MEB
NIH Grant 3R15MH122935-01S1 to JP
University of Nevada: Nevada Undergraduate Research Award to LK

Title: Post-pandemic changes in long-term and working memory behavior

Authors: *M. E. BERRYHILL[1], J. PABLO[1], L. L. KEMMELMEIER[2];
[1]Psychology, Univ. of Nevada, Reno, NV; [2]Psychology, Univ. of Nevada, Reno, Reno, NV

Abstract: In a series of experiments, we revisited two established findings regarding working memory (WM) and its relationship to long-term memory (LTM), and WM retrieval strategy. In both cases, the data counter the prevailing view and suggest that there are behavioral differences in post-pandemic undergraduates. In the first experiment we examined the within-subject correlation between LTM and WM performance. The original goal of this work was to test whether the canonical WM deficits observed in individuals with schizophrenia persist in the subclinical population with variable symptoms associated with schizophrenia (e.g., schizotypy). We collected data from current undergraduates (n=35) on item WM and order WM tasks using complex kaleidoscope images. We also evaluated whether those with higher schizotypy symptom load showed stimulus-dependent LTM deficits. We predicted that if sensory processing differences found in schizophrenia persisted in the subclinical population, the high schizotypy individuals would exhibit worse recognition LTM for visual items (pictures) than for verbal stimuli (words). Across these manipulations the accuracy and reaction time data were null. There was no relationship between schizotypy trait load and WM or LTM performance, regardless of stimuli or task demands. To further explore the data, we then revisited whether there was the expected positive correlation between LTM and WM typical of cognitive models. Instead, we found no significant correlation between LTM and WM. These findings suggest that there may be changes in the behavioral profiles of post-Covid undergraduates. Second, a separate experiment (n=36 undergraduates) probed WM retrieval by comparing performance tested by recall and/or recognition. When the retrieval demands were intermingled and unpredictable, participants performed significantly worse at recall than when they conducted a recall block alone. In other words, they adopted a universal lower-effort recognition strategy rather than a universal high-effort recall strategy, as in previous reports. Finally, the pace of data collection post-Covid remains markedly slower than pre-Covid. This serves as a third piece of evidence that behavioral performance and participant samples may differ from pre-pandemic samples.

Disclosures: M.E. Berryhill: None. **J. Pablo:** None. **L.L. Kemmelmeier:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.25/L11

Topic: H.05. Working Memory

Title: Affect's impact on visual working memory capacity and precision

Authors: C. PICKEN[1], *E. WIEMERS[2];
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Abstract: Everyday our affective states impact our cognition through either enhancement or hindrance of performance. Visual working memory (VWM) is an essential cognitive function serving the maintenance and manipulation of information and can be understood in terms of capacity (the number of items retained) and precision (the quality of what is retained). In order to measure capacity and precision more directly on each trial, we employ a novel task in which participants respond to all items on each trial in any order. In the visual working memory literature, studies have shown that negative affect can enhance visual working memory precision, however, when positive affect conditions were considered, no differences in capacity nor precision were observed. This may be because the visual working memory literature has only induced emotion through positive, neutral, or negative valence images. However, emotion can be understood and induced through a different lens: the motivational dimension. A previous study induced positive affect under this dimension using unexpected reward (i.e. the participant was given a goody bag) prior to a verbal working memory task. Here, increases in capacity were observed. To our knowledge, this method has not been done in any VWM tasks. Thus, the present study utilizes the method of unexpected reward to induce positive affect prior to completing a series of continuous color wheel and arrow-orientation delay-estimation tasks, which assess VWM performance. In addition, we are replicating what has been previously done with negative affect inductions through negative valence images. Consistent with previous findings, we expect to see the negative affect condition show an enhancement in precision. For the positive condition, we expect there to be an enhancement in capacity. Modeling analyses after Zhang and Luck (2008), we find differences in precision and capacity among the three emotional conditions. In sum, the present work employs a VWM task that is more sensitive to participant variability in capacity and precision within each trial and implements a motivational dimension of positive affect. This builds on previous work that mainly focused on negative-valence mood induction, thus we provide a more comprehensive account of affect's effects on visual working memory.

Disclosures: C. Picken: None. **E. Wiemers:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

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Program #/Poster #: PSTR135.26/L12

Topic: H.05. Working Memory

Support: Ann S. Bowers Women's Brain Health Initiative
Alfred P. Sloan Research Fellowship
UCSB Faculty Research Assistant Program
UCSB Undergraduate Research & Creative Activities Grant

Title: Working Memory Precision and Capacity Across Human Menstrual Cycle: a pilot behavioral and eyetracking study

Authors: *Y. LI[1], C. HOLLAND[1], G. BALAGURU[1], H. GROTZINGER[2], E. MURATA[2], E. G. JACOBS[3], T. C. SPRAGUE[4];
[1]Univ. of California, Santa Barbara, Santa Barbara, CA; [2]Psychological and Brain Sci., Univ. of California, Santa Barbara, SANTA BARBARA, CA; [3]UC Santa Barbara, Santa Barbara, CA; [4]Psychological and Brain Sci., UC Santa Barbara, Goleta, CA

Abstract: Working memory (WM) is a fundamental cognitive ability that supports day to day activity (Baddeley, 2010), and is supported in large part by sustained activation levels and patterns in areas of the prefrontal cortex (Funahashi et al, 1989; Emrich et al, 2013; Miller et al, 2021). While previous studies have shown that behavioral performance and prefrontal cortex activation measured during complex WM tasks are correlated with ovarian hormone fluctuation (Jacobs & D'Esposito, 2011), a precise understanding of the impact of ovarian hormones on WM precision and capacity remains unknown. Here, we carefully assayed multiple aspects of visual WM function - WM capacity, precision, response time, and serial dependence - in naturally-cycling female participants. We implemented a dense sampling procedure to collect data from five subjects with regular menstrual cycles approximately every other day throughout one entire menstrual cycle. During each visit, subjects provided saliva samples for measuring ovarian hormones and completed questionnaires regarding their health history, sleep quality, anxiety level and caffeine intake. To characterize WM function, we used both the change localization task (Zhao et al., 2023) to efficiently estimate memory capacity and the memory guided saccade (MGS) task (Funhashi et al, 1989; Li & Sprague., 2023) to precisely characterize visual spatial working memory for one location. For the MGS task, we quantified response time, response precision, and serial dependence (Fischer & Whitney, 2014; Bliss et al, 2017) during each session. Intriguingly, we see evidence supporting dynamic changes in visual WM performance, with change in response time, precision, and magnitude of serial dependence occurring throughout the menstrual cycle. Planned analyses will directly test the impact of ovarian hormone concentrations on WM performance measures (e.g., Pritschet et al, 2021), which will offer a novel behavioral assay of how ovarian hormones impact WM behavior across the menstrual cycle.

Disclosures: Y. Li: None. **C. Holland:** None. **G. Balaguru:** None. **H. Grotzinger:** None. **E. Murata:** None. **E.G. Jacobs:** None. **T.C. Sprague:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.27/L13

Topic: H.05. Working Memory

Title: Case Report: Transcranial Magnetic Stimulation Paired With A Memory Task Has Timing-Specific Effects On An Older Subject

Authors: *A. SAN AGUSTIN[1], J. C. HERNANDEZ-PAVON[2], J. L. PONS[3];
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Abstract: Transcranial Magnetic Stimulation (TMS) induces synaptic plasticity and enhances memory when applied following specific protocols, such as Paired Associative Stimulation (PAS). PAS synchronizes in time and neuronal pathway two stimuli to induce spike-timing-dependent plasticity. Recently, PAS oriented to stimulate hippocampus was shown to improve memory in healthy young subjects (San Agustin, 2023). However, its effect's specificity regarding application time between stimuli has not yet been explored, nor has its effects in older population, which can benefit from memorization enhancement. To address these gaps, we applied PAS in an 87-year-old male subject by pairing a single-pulse TMS with a visual memory task in two different TMS-task timing conditions: 0 ms as in the previous study and 200 ms based on the time in which the hippocampus was activated after seeing a visual stimulus (Mormann, 2008). We also ran a sham TMS condition (3 conditions in total performed in 3 different visits, separated by a week). In the intervention of each condition, 90 pairs of stimuli were applied, divided into three time-blocks of 30 pairs (INT1, INT2, INT3). We assessed memorization capacity at each visit before, during, immediately after, and 30 minutes after the intervention (Baseline, INT1, INT2, INT3, POST, POST30). At each assessment, 30 memory task trials were performed. The task consisted of a matrix presentation with numbers from 1 to 9; then, the numbers disappeared, leaving a white background in the matrix, and finally, the subject had to click on the squares with a white background in ascending order from 1 to 9 to show the remembered location of the numbers. We calculated the proportion of remembered numbers for each trial in each time-block (INT1, INT2, INT3, POST, POST30) compared to the baseline average for that day. Then, we ran a repeated-measures ANOVA with time-block and PAS condition variables. A significant main effect on the PAS condition was revealed ($F(2, 87) = 27.654$, $p < 0.001$). The post-hoc pairwise comparison showed that TMS applied 200 ms after item visualization (Mean = 1.180 SE = 0.036) induced a more significant improvement than TMS applied at 0 ms (Mean = 0.844 SE = 0.036, $p < 0.001$) and sham stimulation (Mean = 0.868 SE = 0.036, $p < 0.001$). This result demonstrates that PAS effects may be TMS-task timing specific. By comparing this result with the study in a young population, which benefited from TMS at a 0 ms timing, we can observe how the effect differs in this older person. This can imply that TMS timing is also specific to the subject's age. A larger sample of elderly participants is necessary to define these effects.

Disclosures: A. San Agustin: None. **J.C. Hernandez-Pavon:** None. **J.L. Pons:** None.

Poster

PSTR135: Behavioral Studies of Working Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR135.28/Web Only

Topic: H.05. Working Memory

Support: PAPIIT-UNAM IN217221 to AERC and PAPIIT-UNAM IN202822 to OPG.

Title: Trait depression, emotional valence, and aging implications for working memory efficency

Authors: *I. GÓMEZ GONZÁLEZ[1], E. LÓPEZ-GONZÁLEZ[2], U. CABALLERO SANCHEZ[3], K. Y. HERNÁNDEZ DUARCA[4], M. MENDEZ DIAZ[5], O. PROSPERO-GARCIA[6], A. E. RUIZ-CONTRERAS[7];
[1]Univ. Nacional Autónoma de México, CDMX, Mexico; [2]LNGC, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [3]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [4]Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [5]Univ. Nacional Autonoma De Mexico, Mexico DF, Mexico; [6]Physiol., Inst. De Neurobiología, UNAM, CDMX, Mexico; [7]Lab. Neurogenomica Cognitiva, Fac. Psicologia, Univ. Nacional Autonoma de Mexico, D.F., Mexico

Abstract: Working memory (WM) is an immediate information store for problem-solving and can be influenced by various factors. One such factor is age: WM efficiency (WME) tends to be lower in older than younger adults. Additionally, depression is known to have a negative impact on WME, with individuals experiencing major depression exhibiting lower WME levels. While there is ample evidence linking state depression to WM, the relationship between trait depression and WME is less clear. It is established that individuals with depression are more attuned to perceiving the negative valence of stimuli and that the perception of emotional stimuli tends to become less negative as people age. This study seeks to investigate the impact of trait depression (TD) on WME in response to emotional valence (EV), particularly examining potential differences between older adults (OA) and young adults (YA). To achieve this, 68 neurologically and psychiatrically healthy volunteers (40 aged 20-29 and 28 over 60) participated in an experimental WM task. During the encoding phase, participants were presented with a face (expressing positive, negative, or neutral EV) and a scene simultaneously for 2000 ms. Participants were instructed to attend to the face and to ignore the scene; after a delay of 4000 ms, during the retrieval phase, participants indicated whether the face was the same or different from the one presented during the encoding phase. Participants also fulfill the State-Trait Depression Inventory. Participants were segregated as a function of age and trait depression levels between medium (36-46) vs. severe (> = 47). As expected, OA presented lower WME than YA, regardless of trait depression. However, there was no difference in WME as a function of trait depression levels. Only for the severe levels of TD, OA had less WME than YA, regardless of EV. For OA with severe levels of TD, WME was worse for negative valence stimuli than for those with positive valence. TD did not have any effect on YA. These findings contribute to our understanding of depression as a trait rather than a disorder. Specifically, OA who frequently exhibit sadness, emptiness, irritability, and despair as their coping mechanism in response to life challenges tend to have lower WME, especially when exposed to negative stimuli. However, there appears to be no significant impact of trait depression during YA.

Disclosures: I. Gómez González: None. **E. López-González:** None. **U. Caballero Sanchez:** None. **K.Y. Hernández Duarca:** None. **M. Mendez Diaz:** None. **O. Prospero-Garcia:** None. **A.E. Ruiz-Contreras:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.01/L14

Topic: H.08. Learning and Memory

Support: Spanish Ministry of Economy and Competitivity PID2021-122446NB-I00

Title: Functional states of prelimbic cortex and related brain centers during the acquisition of a go/nogo task in rats

Authors: *J. DELGADO-GARCIA[1], G. GUTIÉRREZ-PARRAS, Jr.[2], C. ANDREU-SÁNCHEZ[3], M. MARTIN-PASCUAL[4], A. GRUART[5];
[1]Pablo De Olavide Univ., Sevilla, Spain; [2]Univ. Pablo de Olavide, Sevilla, Spain; [3]Univ. Autònoma de Barcelona, Barcelona, Spain; [4]Res. & Develop. RTVE Inst., Res. & Develop. RTVE Instituto. RTVE Corp. Barcelona, Barcelona, Spain; [5]Univ. Pablo de Olavide, Pablo De Olavide Univ., Sevilla, Spain

Abstract: GO/noGO tasks allow to assess decision making processes and the ability to actively suppress a specific action according to the context. In the present experiments, rats had to discriminate between two visual stimuli (GO or noGO) shown in a touchscreen (iPad model), disposed in a horizontal white rectangle (GO) or a vertical green one (noGO). In this situation, the execution (GO) or non-execution (noGO) of the selected action (to touch or not the visual display) were reinforced with a small piece of food. Previously, rats had gone through caloric restriction and maintained to 90% of their initial weight. Rats were trained in a modified Skinner box equipped with an iPad, where stimuli were displayed. The maingoal was to record and to analyze local field potentials (LFPs) collected from cortical and subcortical structures when the visual stimuli were shown and touched in the iPad screen and during the subsequent activities. Animal behavior was videotaped and quantified. The experiment consisted of five phases. Firstly, rats learned to approach the iPad and touch the visual stimuli in the case of GO trials as well as not to touch them during noGO trials. In the next phases, stimuli were mixed in a 50% or a 25%. Results indicate that rats were able of acquiring this rather complicate task with a significant performance even when stimuli were presented at random. Rats were implanted with recording electrodes in five of these sites: motor (MC1) and prelimbic (PrL) cortices, nucleus accumbens septi (NAc) dorsolateral (DLS) and dorsomedial (DMS) striatum, dorsal hippocampus (CA1), mediodorsal thalamic nucleus (MD), and basolateral amygdala (BLA). These brain areas are involved in cognitive and motivational processing, execution of motor responses, and contribute to reward-directed behaviors. Spectral power changes during performance of the task were observed mainly in delta, theta and gamma bands. A detailed analysis of LFP activities recorded in the PrL cortex and in other cortical (MC1, CA1) and subcortical (NAc, BLA, DMS, DLS, and DM) areas during the acquisition and performance of a GO/noGO task further supports a selective modulation of neural activities during cognitive vs. locomotor or stationary behavioral activities, depending on the learning stage of the experimental animal. In particular, PrL spectrograms were specifically different for correct vs. incorrect GO and noGO responses, while MC1, CA1 and DLS spectrograms were more related to the motor

components of the selected behavior. Thus, these brain areas are selectively involved in cognitive and motivational processing, execution of motor responses, and/or contribute to reward-directed behaviors

Disclosures: J. Delgado-Garcia: None. **G. Gutiérrez-Parras:** None. **C. Andreu-Sánchez:** None. **M. Martin-Pascual:** None. **A. Gruart:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.02/L15

Topic: H.08. Learning and Memory

Support: Natural Sciences and Engineering Research Council of Canada Discovery Grant (RGPIN-2021-02569)

Title: Memory transformation and reorganization of the motor memory network over time

Authors: *H. NEVEU KARIMPOUR[1], M. LILLEY[1], K. SINCLAIR[1], M. SHELTAMI[1], N. ABUOSBA[1], M. BRADLEY-GARCIA[1], E. DUBÉ-ZINATELLI[1], M. R. HOLAHAN[2], M. J. SEKERES[1], H. DANBY[1];
[1]Psychology, Univ. of Ottawa, Ottawa, ON, Canada; [2]Dept. of Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: This study investigates motor memory transformation and the reorganization of the motor memory network over time. While the acquisition of a new motor skill is typically viewed as independent of episodic memory, the unique experience of first learning that skill results in the formation of a new event memory. Using a confirmatory approach, we aimed to disentangle the episodic memory experience of skill acquisition from the motor memory component to clarify systems consolidation and neural network reorganization in motor memories. We examined how neural activity in key brain structures involved in the consolidation of motor memories, such as the hippocampus (HPC), medial prefrontal cortex (mPFC), motor cortex, striatum, and basal ganglia, reorganizes over time to support the transformation of motor memory as a novel skill becomes familiar and habitual. Male and female C57BL/6N x 129Svev wild-type mice, aged 8 to 12 weeks, were assigned to one of six conditions: homecage control (no experimental manipulation), training only (motor task without further testing), recent (recent novelty), remote (remote unpracticed memory), continuous (remote highly familiar memory), and continuous context-shift (familiar task in a novel context) motor training. These conditions were designed to control for the major influences of memory, including time, context, and familiarity. Mice underwent training on a novel Rotorod motor task according to their assigned condition. Ninety minutes after the final motor testing trial, mice were perfused, and their brains were processed for immunohistochemical labeling of c-Fos as a marker of neuronal activity. c-Fos cells expression in the various brain regions of interest was assessed through stereological

counting. Behavioral data analyses, conducted using two-way ANOVAs, revealed a significant increase in latency to fall on testing day compared to training day in both the remote ($p < .05$) and continuous ($p < .05$) conditions, emphasizing the role of time and practice in motor memory retrieval. Preliminary analyses of c-Fos count data in the CA1 and DG regions of the HPC, performed with a two-way ANOVA, revealed no significant difference ($p > .05$) between the continuous and remote conditions, indicating sustained hippocampal engagement regardless of motor memory familiarity. These findings suggest consistent reorganization across declarative (episodic) and non-declarative (motor) memory, possibly indicating memory transformation as a fundamental consolidation process.

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Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.03/L16

Topic: H.08. Learning and Memory

Title: Pre-exposure Lateral Orbitofrontal Cortex Activation or Inactivation on Latent Inhibition of Fear Learning

Authors: *T. WANG;
Inst. of Systems Neurosci., Hsinchu, Taiwan

Abstract: <META NAME="author" CONTENT="姿穎 王">**Pre-exposure Lateral Orbitofrontal Cortex Activation or Inactivation on Latent Inhibition of Fear LearningAuthors*Tzu-Ying Wang**, Chun-hui Chang; Institute of Systems Neuroscience, National Tsing Hua University, Hsinchu, Taiwan 30013**DisclosuresTzu-Ying Wang**: None. **Chun-hui Chang**: None.**Abstract**Latent inhibition (LI) is a phenomenon that presenting a stimulus several times without consequences leads to the delay of subsequent conditioning to that stimulus. The development of LI reflects a process of learning to ignore the irrelevant stimuli. LI deficits have been reported in acute schizophrenia patients, and these patients are accompanied with hypoactivation of the orbitofrontal cortex (OFC). Previously, studies in our lab have demonstrated that activation of the lateral OFC (lOFC) mimicking obsessive-compulsive disorder (OCD) condition impaired several aspects of fear learning and expression. However, how inactivation of the lOFC mimicking acute schizophrenia condition interacts with LI remains unknown. Therefore, we aimed to study how activation or inactivation of the lOFC during tone pre-exposure session of the LI procedure would influence the acquisition of cue-induced fear in male Long-Evans rats using freezing as the behavioral readout. In Experiment 1, we first confirmed that the animals would acquire LI after two days of tone pre-exposure (45 tones only; 10s, 2 KHz, 85 dB, inter-trial interval [ITI] of 30s), followed by fear conditioning on

Day 3 (5 tone-shock pairings; 2s footshock, 1.0mA, co-terminated with the 10s tone, ITI of 60s) and test on Day 4 (45 tones only, ITI of 30s). In Experiment 2, the same behavioral procedures were applied, while the lOFC was activated with NMDA (1.5 μg/μl, 0.5 μl/side) or inactivated with GABAA/GABAB agonist cocktail consisting of muscimol and baclofen (0.25 μg/μl each, 0.5 μl/side) during the two days of tone pre-exposure. Our results confirmed that animals underwent two days of tone pre-exposure rendered their ability to acquire conditioned fear to the tones compared to no-exposure controls. Moreover, lOFC inactivation during pre-exposure led to deficit of LI that these animals showed freezing level in between the pre-exposure and no-exposure controls during test. We also found that lOFC activation during pre-exposure resulted in greater LI that these animals showed lower freezing level than the pre-exposure controls during test. Together, our results indicated that animals with aberrant lOFC activation level negatively impacted their processing of irrelevant stimuli as shown in LI
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Disclosures: T. Wang: None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.04/L17

Topic: H.08. Learning and Memory

Title: Learning and use of reward-related representations across cortex and time

Authors: *A. S. TONG[1], V. SREEKUMAR[2], S. K. INATI[3], K. A. ZAGHLOUL[3], M. W. WOOLRICH[1];
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Abstract: Reward-related representations are found distributed throughout many human subcortical and neocortical regions that support different neural processes. These representations get used at different points in time for related tasks. However, the way these representations get used and change with learning is not well understood. To investigate this, we recorded from the temporal lobe and prefrontal cortex with intracranial electrocorticography while human subjects learnt two-choice decisions across two different scenes. Crucially, subjects were sometimes able to straightforwardly re-use knowledge, but only when the reward contingencies stayed the same between the two scenes. Using a Bayesian learner, we inferred reward expectations from choice behavior, and then measured representations of these expectations in electrocorticography data. First, we found that reward expectations were uniquely represented in multiple, distributed regions across the human subcortex and neocortex. Second, we found that the representations of reward expectation in the medial temporal lobe and orbitofrontal cortex were re-used between the two scenes, but only when the subjects could straightforwardly transfer knowledge between the two scenes. Finally, we found that in the anterior temporal lobe, the strength of reward

representations, as measured by their similarity between scenes, increased as learning increased. Our findings suggest that patterns of activity representing reward information are integrated into multiple brain regions, get re-used in similar situations, and increase in fidelity with learning.

Disclosures: A.S. Tong: None. **V. Sreekumar:** None. **S.K. Inati:** None. **K.A. Zaghloul:** None. **M.W. Woolrich:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.05/L18

Topic: H.08. Learning and Memory

Support: NIH R01MH129492

Title: Dynamics of neural representations during the learning of compositional tasks

Authors: *Q. HE, S. TAFAZOLI, T. BUSCHMAN;
Princeton Univ., Princeton, NJ

Abstract: Human and other animals are efficient learners, leveraging prior task knowledge to accelerate acquisition of new tasks. We have recently shown that that the brain can flexibly perform multiple tasks by compositionally combining task relevant shared neural representations across tasks. This compositionality enhances learning efficiency, allowing neural circuits to be repurposed across different tasks. However, any alterations in these circuits during one task can potentially affect all tasks associated with them, raising the important question of how we are able to harness existing knowledge to tackle new tasks while avoiding potentially catastrophic interference between the new task and previously learned tasks. To begin to answer these questions, we conducted chronic recordings of neural activities from the prefrontal cortex of rhesus macaques as they learned a new task while also performing three previously learned tasks. All four tasks involved categorizing visual stimuli based on either shape or color and indicating responses via saccadic movements along two response axes. In Task S1 or S2, the animals categorized a stimulus based on its shape and responded with a saccade to the upper-left/lower-right or upper-right/lower-left locations, respectively. In Task C1 or C2, the same stimulus was categorized by its color and the animal indicated their decision with an upper-left/lower-right or upper-right/lower-left saccade, respectively. Monkeys were performing well on S1, C1 and C2 prior to learning task S2. We recorded daily activities from stable populations of neurons throughout the entirety of the monkey's learning of the S2 task. Our preliminary analysis shows rather than smoothly transferring acquired skills from previous tasks, learning a new task led to a decline in performance of previously learned compositionally related tasks. Furthermore, neuronal selectivity for various task features fluctuated from day to day during the initial stages of learning. On the population level, we observed a gradual convergence of neuronal subspaces

for different task as the monkeys learned the new rule. Overall, our results suggest a dynamic interaction between task representations while learning a new task.

Disclosures: Q. He: None. **S. Tafazoli:** None. **T. Buschman:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.06/L19

Topic: H.08. Learning and Memory

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MEXT Promotion of Distinctive Joint Research Center Program Grant Number JPMXP0621467950

Title: Memory schema reorganization as a deliberating process in the central executive network

Authors: *H. KURASHIGE[1], J. KANEKO[2], K. MATSUMOTO[3];
[1]Tokai Univ., Minato-ku, Japan; [2]Sch. of Information and Telecommunication Engin., Tokai Univ., Minatoku, Japan; [3]Brain Sci. Inst., Tamagawa Univ., Machida, Japan

Abstract: When people encounter information incongruent with their existing knowledge or schema, they may need to reorganize their schema to incorporate the information into them. Such a phenomenon is called schema accommodation. Schema accommodation is an important but less likely phenomenon than schema assimilation, in which schema-congruent information is assimilated without substantial changes to the schema itself. This makes the neural basis of schema accommodation difficult to elucidate. To identify it, reorganization of the existing schema must occur with sufficient certainty. To this end, we conducted an fMRI experiment using a paradigm we termed the reversal description task. On the first day, participants were given a document, asked to read it carefully, and then to write a text summarizing their understanding. The document was difficult to understand and required active interpretation. The next day, after re-reading and re-writing, participants were asked to answer a two-choice question where the answer depended on their interpretation. Then they were told that the opposite of their chosen option was the 'correct' answer. Participants were required to change the interpretations of the document to make a 'correct' answer during the fMRI scan and to write a text again after the scan. During the fMRI scan, the participants were asked to reconsider the sentences in the document re-presented to them and to answer at the push of a button whether the interpretations of the sentences had changed or not. This classified trials with and without schema accommodation. For the participants who changed their interpretation, there was greater activity in the left central executive network (CEN), consisting of the middle frontal gyrus and inferior parietal lobule, and the left superior frontal gyrus on trials that exhibited schema accommodation than on trials that did not. Additionally, we observed a significant

psychophysiological interaction between those regions and the left and right lateral occipital cortex. Those networks are considered to be involved in deliberative processing such as cognitive control and attention. In contrast, the ventromedial prefrontal cortex (vmPFC) showed greater activity in trials without schema accommodation. Since the vmPFC is involved in schema assimilation and its activity is often anticorrelated with that of the CEN, those results suggest the schema accommodation-to-assimilation axis that can align with the competitive activity between the CEN and default-mode network. It may indicate complementary roles of them in schema-dependent knowledge acquisition: fast autonomous assimilation and slow deliberative accommodation.

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Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

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Program #/Poster #: PSTR136.07/L20

Topic: H.08. Learning and Memory

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Swiss National Science Foundation (B.F.G. CRSII5-173721 and 315230 189251)
ETH project funding (B.F.G. ETH-20 19-01)
Human Frontiers Science Program (RGY0072/2019)

Title: Adaptive Neuronal Populations in Medial Prefrontal Cortex During Flexible Avoidance Learning

Authors: *A. VO[1,2], B. EHRET[3], R. BOEHRINGER[3], E. ABS[3], P. EUGSTER[3], B. F. GREWE[1,2];
[1]ETH AI Ctr., ETH Zurich, Zurich, Switzerland; [2]Institute of Neuroinformatics, University of Zurich and ETH Zurich, Zurich, Switzerland; [3]Inst. of Neuroinformatics, Univ. of Zurich and ETH Zurich, Zurich, Switzerland

Abstract: To survive, animals need to adjust to changing threat cues mediated by neuronal circuits that allow such rapid, adaptive behaviour. The medial prefrontal cortex (mPFC) is crucial for computing avoidance responses [1, 2, 3, 4], yet the neural mechanisms for rapidly adapting to different threats remain unclear. To adress this gap, we investigate mPFC neuronal dynamics during flexible avoidance learning using mobile population calcium imaging in mouse mPFC. Initially, mice learned to avoid an aversive foot shock associated with conditioned tone stimulus CS1 (Task 1). After a task switch, a second stimulus CS2 then signaled the upcoming shock (Task 2). Using single-cell analysis we found a larger fraction of cells responsive to both CS1 and CS2 after the task switch in mice mastering both tasks (Switchers) compared to those proficient in only Task 1 (Non-Switchers). We termed these as “adaptive cells”, as they exhibited

a dynamic shift from predominantly CS1 responsiveness in Task 1 to dual-tone responsiveness (CS1 and CS2) in Task 2 (see Fig. 1). Further, our population decoding analysis unveiled a prominent role of these adaptive neurons in shaping behavioral outcomes. In summary, using an active avoidance task with a switch of the CS, we identified the existence of adaptive neuronal populations and uncovered their contributions in encoding sensory stimuli and in shaping avoidance behavior.

References: [1] Le Merre et al. 2021, [2] Jercog et al. 2021, [3] Martin-Fernandez et al. 2023, [4] Ehret et al. 2023

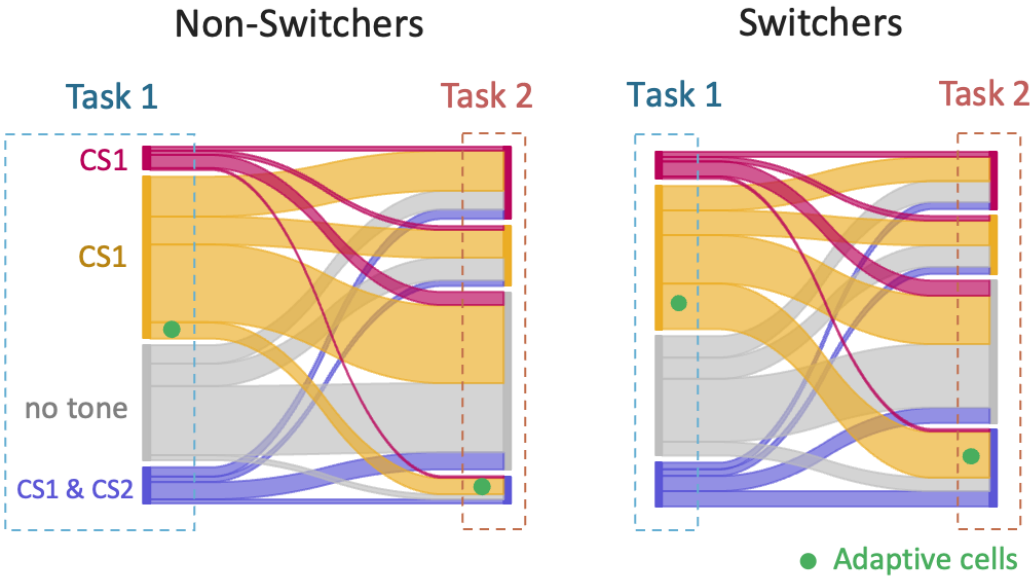

Figure 1: Development of responsiveness of cells to either CS1, CS2, no tone or CS1 & CS2 from Task 1 to Task 2 for Non-Switchers (left) and Switchers (right). Switchers show a larger amount of adaptive cells (green marker) compared to Non-Switchers.

Disclosures: A. Vo: A. Employment/Salary (full or part-time):; ETH AI Center, ETH Zurich. **B. Ehret:** None. **R. Boehringer:** A. Employment/Salary (full or part-time):; Institute of Neuroinformatics, University of Zurich and ETH Zurich. **E. Abs:** A. Employment/Salary (full or part-time):; Institute of Neuroinformatics, University of Zurich and ETH Zurich. **P. Eugster:** A. Employment/Salary (full or part-time):; Institute of Neuroinformatics, University of Zurich and ETH Zurich. **B.F. Grewe:** A. Employment/Salary (full or part-time):; Institute of Neuroinformatics, University of Zurich and ETH Zurich.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.08/L21

Topic: H.08. Learning and Memory

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22H00432
22K06468
20K06934
23K06344
Brain/MINDS
22KJ0812

Title: In vivo two-photon Ca2+ imaging reveals distinct neural activity dynamics during fear memory formation and recall in the deep layers of the prelimbic cortex

Authors: *H. KONDO, R. KIM, R. SHIMODA, K. INOKUCHI, Y. KONDO, M. OKAMURA, K. OTA, H. FUJII, H. BITO;
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Abstract: The prelimbic cortex (PrL), a subregion of the medial prefrontal cortex, is known to be essential for the recall of fear memory. Of particular interest is the single neuron and ensemble activity in layer V of the PrL, as these neurons directly project to critical regions for fear response such as the basolateral amygdala (BLA) and the periaqueductal gray (PAG). However, how deep layer neurons in the PrL specifically contribute to fear memory formation and recall has remained elusive, due to their > 1.5 mm depth from the brain surface dura mater hampering access to multiphoton microscopy. Here we developed an oblique GRIN lens insertion route that enabled *in vivo* deep-brain two-photon Ca2+ imaging. Longitudinal recordings of neuronal activity from neurons primarily in layer V of the PrL (495-590 μm from midline) were performed at a single-cell resolution (lateral and axial PSFs were 0.88 μm and 10.35 μm, respectively) throughout the formation and recall of fear memory. Using a head-fixed auditory fear conditioning paradigm, we identified a neuronal ensemble in deep layers of the PrL that specifically associated with fear recall. Indeed, about 21% of recorded neurons from the deep layers of the PrL showed an enhanced response during the conditioned stimulus (CS), when compared before and after auditory fear conditioning. Furthermore, this neuronal ensemble also exhibited significantly stronger responses during the brief memory forming epochs when auditory stimuli (CS) and foot shocks (unconditioned stimulus, US) were co-presented, while such an increase was not shown in the other neurons ($p < 0.001$ in a two-way RM ANOVA for the factor of ensemble type). Conversely, neurons displaying a significantly strong response during the co-presentation periods were significantly more likely to be recruited into a cell ensemble during fear recall ($p < 0.001$, Two-sided Fisher's exact test). Together, these findings suggest the possibility that neural activity during fear memory formation, and more specifically during CS-US co-presentation, may influence future fear memory recall, perhaps via an activity-dependent adaptation of an ensemble activity in layer V of the PrL. Thus, this study clarifies hitherto unknown characteristics of activity dynamics patterns, and shed light on emerging cell ensembles, in the deep layer of the PrL during new fear memory formation and recall.

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Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.09/L22

Topic: H.08. Learning and Memory

Support: NIH Grant 5R25DA057786
NIH Grant F31DA053706
NIH Grant R37DA032750

Title: Tracking PFC Dopamine Dynamics During Reversal Learning

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Abstract: An important part of recovery from substance use disorder is degrading high value associations between drug cues and the drugs themselves. Dopamine plays a crucial role in learning, and is specifically implicated in the prefrontal cortex (PFC) and reversal learning (Kosaki & Watanabe, 2012) - learning to update and change behavior when cue contingencies change. Past studies have reported elevations in dopamine during contingency reversal (Van der Meulen et al., 2007), but the timescale of how activity of PFC dopamine neurons maps to reversal learning remains unclear. Here we investigated the activity of PFC dopamine during reversal learning in a longitudinal fiber photometry study, recording dopamine signal on a timescale of seconds. Eight C57/BL6 mice were injected in the mPFC with AAV2/9-hSyn-GRABDA3h (Zhuo et al., 2023) which was followed by implantation of a photometry fiber.Then, the mice were trained on a reversal learning task where they initially learned that two of four presented odors (85-85and85-15) precipitated a sucrose reward in 85% of the trials while the remaining two odors (15-15and15-85) precipitated the reward for only 15% of the trials. Once the learning was stable, reward probability flipped for two odors (one 85% odor (85-15) and one15% odor (15-85)) and the mice updated their behavior to the new odor/reward structure. We conducted fiber photometry recordings of PFC dopamine dynamics during pre-reversal, reversal, and post-reversal stages. Our data replicate findings by Van der Meulen et al. (2007) demonstrating elevated dopamine release during the reversal period, and localize this release as centered around the 15-85cue(contingency enhancement). GLM-mediated analysis of the relationship between the dopamine signal and behavior also revealed significant cue, reward prediction error, and15-85reversal coding in the majority of animals, suggesting a multi-faceted role for dopamine in the PFC. Given this, dopamine in the PFC may play an important mediating role in the enhancement of associations between drugs and drug cues, but does not play a clear role in contingency degradation.

Disclosures: Z.Q. Garrett: None. **M. Hjort:** None. **G.D. Stuber:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Topic: H.08. Learning and Memory

Support: NIH Grant R01 HD110541
NIH Grant R01 HD095966

Title: Early-life prefrontal cortex inhibition and early-life stress lead to long-lasting behavioral, transcriptional, and physiological impairments

Authors: E. D. MENEZES, **L. RACHMANY**, F. FRANCISCA DE ABREU, *C. TEIXEIRA; New York Univ. - NKI, New York, NY

Abstract: Early-life stress has been linked to multiple neurodevelopmental and neuropsychiatric deficits. Our previous studies have shown how maternal presence/absence from the nest in developing rat pups have led to changes in prefrontal cortex (PFC) activity. We have shown that these changes are modulated by serotonergic signaling. Here we test whether changes in PFC activity during early life affect the developing cortex leading to behavioral alterations in the adult. We show that inhibiting the PFC of mouse pups leads to cognitive deficits in the adult similar to those seen following maternal separation. We also show that activating the PFC during maternal separation can prevent these behavioral deficits. To test the effects of maternal separation on transcriptional profile of the PFC, we performed single-nucleus RNA-sequencing. Maternal separation led to differential gene expression almost exclusively in inhibitory neurons. In addition, we found changes in GABAergic and serotonergic pathways in these interneurons. Interestingly, both maternal separation and early-life PFC inhibition led to changes in physiological responses in prefrontal activity to GABAergic and serotonergic antagonists that were similar to the responses of more immature brains. Prefrontal activation during maternal separation prevented these changes. These data emphasize a crucial role of PFC activity and development that manifests in adult behavior.

Disclosures: E.D. Menezes: None. **L. Rachmany:** None. **F. Francisca de Abreu:** None. **C. Teixeira:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.11/L24

Topic: H.08. Learning and Memory

Support: NIH Grant R01-MH111703

Title: Behavioral and neural correlates of learning when predictable rules are mixed with random reinforcement

Authors: *Y. JIN[1], G. G. JENSEN[2], J. P. GOTTLIEB[3], V. P. FERRERA[3];
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Abstract: Humans as well as animals are constantly learning novel predictable relationships to better adapt to the environment. However, such "learnable" patterns are often intermixed with noisy "unlearnable" randomness and it is not known to what degree organisms can differentiate them when these two are presented simultaneously. Here, we exposed both humans (N=160) and primates (N=5) to two pictorial sets: a "learnable" set in which the stimuli were implicitly ordered and the correct response was always to choose the higher-rank stimulus, and an "unlearnable" set in which stimuli were unordered and feedback was random regardless of the choice. Surprisingly, the behavior patterns under the two sets were extremely polarized: Some humans ordered the stimuli in neither set (non-learners). Other humans, as well as all monkeys, ordered the stimuli in both sets, learning the correct order from the learnable set while behaving as though some ordering also existed from the unlearnable set. Neural recordings in the dorsal anterior cingulate cortex (dACC, 24c, N=280) showed that neurons responded predominantly during choice selection or after feedback delivery and encoded learnability, reward value, and their interaction. Particularly during the second half of the session when behavior was stable, a population of neurons (23.5%) appeared to encode the objective rank and prediction error in the learnable context or the fictitious rank and subjective prediction error in the unlearnable context. Both behavioral and electrophysiology results suggest that human and monkeys did not differentiate well between real (learnable) patterns as opposed to random reinforcement, which contributes to deeper understanding of multi-rule learning and the formation of persistent superstitious biases.

Disclosures: Y. Jin: None. **G.G. Jensen:** None. **J.P. Gottlieb:** None. **V.P. Ferrera:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR136.12/L25

Topic: H.08. Learning and Memory

Support: University of San Diego

Title: Spatial decision-making deficit and neuroinflammation in the medial temporal lobe in a rodent model of ADHD

Authors: Z. WYNTER, M. WYATT, M. KRAMER, G. FERNANDES, S. SKUBIC, *J. B. HALES;
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Abstract: The ability to remember locations of objects and make navigational decisions is critical for moving through our environment. Unfortunately, these tasks can be considerably more difficult for individuals with certain neurological conditions, such as attention deficit hyperactivity disorder (ADHD). In order to explore this complex cognitive behavior, our lab has used the Traveling Salesperson Problem (TSP), which examines naturalistic spatial foraging in rats. TSP is an optimization task that requires subjects to identify the shortest route to travel from a starting to ending point while visiting a certain number of targets in an open arena. This spontaneous behavior involves multiple cognitive processes, including spatial working memory, decision-making, route planning, and navigation, and previous research from our lab has found that rats with damage to the hippocampus and medial entorhinal cortex (MEC) show deficits in measures of spatial memory on the TSP. Interestingly, people with ADHD have shown similar working memory deficits. Although animal models cannot fully reflect human neurological conditions, they can provide insight into the disorder that cannot be obtained from human studies. Our study examined the performance of male and female Spontaneously Hypertensive Rats (SHR), the most widely used rodent model of ADHD, relative to their control model, Wistar Kyoto (WKY) rats, on the TSP task. In both rodent and human studies of ADHD, females have been understudied, exacerbating the critical need to examine sex as a biological variable. Our behavioral findings suggest that both male and female SHR have greater deficits in spatial decision-making and route planning compared to WKY rats. Preliminary histological results suggest differential microglia expression and activation, a marker of inflammation, in male and female WKY and SHR rats in brain regions of interest, such as the hippocampus and prefrontal cortex.

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Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.13/L26

Topic: H.08. Learning and Memory

Support: TRIO McNair
University of San Diego
Prebys Foundation Grant

Title: The role of the medial prefrontal cortex in memory and spatial navigation in the traveling salesperson problem in rats

Authors: J. SPAULDING[1], ***M. TAVARES**[2], L. KAZANJIAN[1], A. EHRLICH[1], R. BLASER[1], J. B. HALES[1];
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Abstract: Cognitive impairments, including memory loss, disrupted spatial navigation, and poor executive function, are devastating features of many neurological conditions. Effective research into the causes and treatments of such disorders requires knowledge of the neurological mechanisms that underlie these cognitive processes. Our lab has used the naturalistic spatial foraging task known as the Traveling Salesperson Problem (TSP) to examine these processes in rodents. The TSP is an optimization task that requires subjects to identify the shortest route to travel between a certain number of targets. Previous studies from our lab have found that rats with hippocampal lesions and medial entorhinal cortex lesions are impaired across many different measures in the TSP task, specifically on measures of spatial memory but not spatial decision making. Given the various cognitive demands of this task, our lab was interested in examining the role of the medial prefrontal cortex (mPFC) in the TSP. We also investigated sex as a biological variable in rodent performance on the TSP by testing both male and female rats following excitotoxic lesions of the mPFC or sham lesions. Historically, animal studies have predominantly focused on males, with the justification that female hormone fluctuations throughout the estrous cycle were believed to introduce increased variability in physiological, cellular, and behavioral measures. As a result, empirical data concerning sex differences and factors underlying disease progression in females is limited. The negative consequences of this practice can be clearly seen in our clinical understanding of various medical conditions and how current systems for evaluation, diagnosis, and treatment are still optimized for male, and not females, patients. Therefore, there is a strong need to better understand the neurobiological mechanisms and systems underlying sex-related differences in cognitive functions. Our preliminary results showed an interaction between mPFC lesions and sex in rat performance, with mPFC-lesioned males, but not females, traveling on a less optimal path between targets. Our results suggest a potential differing role of the mPFC in spatial navigation in female and male rats.

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Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.14/L27

Topic: H.08. Learning and Memory

Support: Alzheimer Nederland: WE.03-2020-05

Title: The role of parvalbumin interneurons in cortical memory engrams in a mouse model of Alzheimer's disease

Authors: *J. J. VAN ADRICHEM[1], M. C. VAN DEN OEVER[2], A. B. SMIT[3], R. E. VAN KESTEREN[4];
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Abstract: Memories are stored by sparse populations of neurons, i.e. engram cells, which increase their connectivity upon learning. Whereas recent memories are stored by hippocampal engrams, engram cells in the medial prefrontal cortex (mPFC) are responsible for memory persistance. Whether a neuron is recruited into an engram depends on its excitability during learning. Interestingly, parvalbumin (PV) interneurons in the CA1 of APP/PS1 mice, a mouse model of Alzheimer's disease (AD), show altered excitability. However, it is unclear whether cortical interneurons alter engram persistence, and how this contributes to remote memory decline in AD. APP/PS1 and wild type mice were exposed to contextual fear conditioning (CFC) and active cells in the mPFC were tagged using viral-TRAP. Remote memory retrieval was tested 4 weeks after CFC and brains were isolated for immunohistochemistry. Furthermore, excitability of PV interneurons and pyramidal neurons in the mPFC was studied using patch-clamp recordings in APP/PS1 mice. Remote memory retrieval was impaired in 20-week-old, but not 16-week-old, APP/PS1 mice. Accordingly, PV cells in the mPFC of APP/PS1 mice showed an increase in AP frequency in response to current steps in APP/PS1 mice at 20, but not at 16 weeks. At both ages, no genotypic differences were observed in the labeling, activation and reactivation of engram cells, and the proportion of (re)activated PV cells did not differ between genotypes. Remote memory retrieval deficits at 20, but not at 16, weeks points to a progressive decline in remote memory function in APP/PS1 mice. While no alterations were observed at the cellular engram level, memory deficits at 20 weeks coincided with mPFC PV cell hyperexcitability. Whether mPFC PV cell hyperexcitability is causally related to remote memory impairment in APP/PS1 mice is currently under investigation. Furthermore, we will examine whether PV cell hyperexcitability alters synaptic connectivity within cortical memory engrams.

Disclosures: J.J. van Adrichem: None. **M.C. Van den Oever:** None. **A.B. Smit:** None. **R.E. Van Kesteren:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.15/L28

Topic: H.08. Learning and Memory

Support: NWO Zwaartekracht Brainscapes

Title: Fear conditioning intensity-dependent differences in the engram circuitry and spine properties of cortical engram cells

Authors: *S. BEERENS, A. B. SMIT, M. C. VAN DEN OEVER;
Mol. and Cell. Neurosci., Ctr. for Neurogenomics and Cognitive Res., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: Accumulating evidence indicates that memory persistence depends on reactivation of sparsely distributed cortical neurons that are defined during learning, so-called engram cells. In line with this, we previously reported that neurons in the prelimbic cortex (PL) that are activated during contextual fear conditioning (CFC) are required for remote memory expression. However, their causal involvement depends on the intensity of a fearful experience, such that CFC-activated PL neurons are engaged in remote memory after a mild (1 foot-shock, 1US), but not strong (3 foot-shocks, 3US), fearful experience.
We previously explored the electrophysiological and structural synaptic properties of engram cells after 1US and 3US CFC. We found increased presynaptic release probability onto 1US and 3US engram neurons combined with a selective increase in spine density on the proximal apical dendrite of 1US engram cells compared to non-engram cells. The latter was not present on 3US engram neurons. However, whether the 1US increase in spine density is represented by mature or immature type of spines remained to be determined.
Here, we investigated the spine morphology of engram and non-engram neurons at a remote timepoint after mild and strong CFC by 3D reconstruction of proximal apical dendrites. We found that the increase in spine density for 1US engram neurons is explained by an increase in spine density for more immature type of spines, i.e. stubby and thin spines. Overall, this points to increased plasticity of specific synaptic connections on the proximal apical dendrite of 1US, but not 3US, cortical engram cells, in agreement with the PL engram being functionally involved in mild fear memory retrieval only.
The selective increase in spine density and functional involvement of PL 1US engram neurons suggests that engram circuitry that engages the PL might be dependent on intensity of the fearful experience. Therefore, we retrogradely labeled PL-projecting engram neurons after 1US and 3US CFC. Additionally, we explored the functional network during remote retrieval of 1US and 3US CFC. To do this, we quantified the number of Fos-expressing cells during remote retrieval across a variety of brain regions. We then performed a network analysis on strong correlations to identify differences in the 1US and 3US memory retrieval network. Taken together, we found differences in brain regions that have a central position in the correlation networks of 1US and 3US retrieval, indicating that the neural circuitry involved in mild and strong fear memory retrieval is distinct.

Disclosures: S. Beerens: None. **A.B. Smit:** None. **M.C. Van den Oever:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

Location: MCP Hall A

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Program #/Poster #: PSTR136.16/L29

Topic: H.08. Learning and Memory

Title: Astro-grasp: identification of changes in astrocyte-synapse interaction on persistent memory engram cells

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Ctr. for Neurogenomics and Cognitive Res. (CNCR), Vrije Univ., Amsterdam, Netherlands

Abstract: Astrocytes and neuronal synapses function as bidirectional partners in the modulation of synaptic transmission. We previously showed that retraction of hippocampal perisynaptic astrocytic process (PAPs) has an important role in memory processing. However, it is not known whether these changes in PAP-synapse interaction are different for engram versus non-engram neurons. Here we present a new tool referred to as Astro-GRASP (enhanced green fluorescent protein reconstitution across synaptic partners), that enables us to study the contact between PAP and engram synapses. With Astro-GRASP, we aim to gain new insight in the PAP-synapse interaction overtime and how this contributes to engram specific synaptic alterations relevant for memory persistence. During fear learning, a small population of neurons in the prelimbic cortex (PL) is activated and these specific neurons are required for remote memory retrieval, thereby forming an engram ensemble. Here, we analyzed the caudal anterior cingulate cortex (cACC) to PL projection, for which a neuronal cyan-pre-eGRASP was injected in the cACC and a neuronal myrRFP-post-eGRASP together with an astrocytic YFP-pre-eGRASP construct was expressed in the PL. Contextual fear conditioning (CFC) was performed to create a persistent cortical fear memory engram. We were able to separately label the general and engram neuronal population in the cACC and PL, and study differences in astrocytic contacts with cACC synapses on PL neurons. Together, Astro-GRASP allows comparison of astrocytic contacts and synaptic characteristics between the general and engram cACC projection to the PL at a recent and remote time point after learning.

Disclosures: A. Mak: None. **A.B. Smit:** None. **M.H. Verheijen:** None. **M.C. Van den Oever:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.17/L30

Topic: H.03. Decision Making

Support: ERC StG MEMCIRCUIT 758032
ONE MUNICH Strategy Forum Next Generation Human-Centered Robotics

Title: Dynamic prefrontal neuronal representations in association learning

Authors: *Y. HUANG[1,2], L. S. MEHRKE[1], T. W. BERNKLAU[1], L. BUSSE[2], S. N. JACOB[1]; [1]Translational Neurotechnology Laboratory, Dept. of Neurosurg., Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [2]Biol. II, LMU Munich, Planegg-Martinsried, Germany

Abstract: During associative learning, animals generate internal concepts of their environment and flexibly link sensory stimuli, actions and outcomes. In rodents, the medial prefrontal cortex (mPFC) is believed to play an important role in this process. However, how prefrontal neurons represent sensory variables and convert these to behavioral choices under changing task demands is unclear. Here, we trained head-fixed mice to form stimulus-action-outcome associations with implicit rule switches, requiring the animals to choose left or right according to the location or frequency of an auditory cue. As the animals acquired the task, we recorded from the mPFC (prelimbic area) using chronic single-photon fluorescent calcium imaging with cellular resolution (head-mounted miniature microscopes, "miniscopes"; GCaMP6f targeted to excitatory projection neurons). We were able to follow n = 170 (out of n = 1100 total) neurons over the course of several months (n = 4 animals). 93 % of neurons recorded across all imaging sessions showed task-related activity at various timepoints throughout the trial. The epochs of task-related activity were neuron-specific and remained the same across tasks. Selectivity of the neuronal population for the currently relevant sensory cue dimension was gradually established during training and shifted to the other dimension after the task rule switched. Activity of individual neurons was predominately triggered by a single sensory dimension within a session. Further analyses revealed that this activity represented the animals' behavioral choice (response to the left or right), rather than the sensory properties of the cues. Interestingly, selectivity in the majority of these neurons peaked in individual sessions and was relatively weak in others. A small subset of neurons exhibited shifts in selectivity in conjunction with changes in the task rule. This pattern suggests the presence of a hub-like structure within the neuronal population that gives rise to a task-adapted low-dimensional representation. We will next explore dimensionality reduction approaches to identify neurons that contribute most strongly to the encoding of behavioral choices and characterize in depth their anatomical (spatial) and functional (connectivity) relationship to the entire mPFC neuronal population. In conclusion, we found a low-dimensional representational structure in mouse mPFC for the dynamic encoding of adaptive choices under changing task demands.

Disclosures: Y. Huang: None. **L.S. Mehrke:** None. **T.W. Bernklau:** None. **L. Busse:** None. **S.N. Jacob:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Program #/Poster #: PSTR136.18/L31

Topic: H.03. Decision Making

Support: ERC StG MEMCIRCUIT 758032

Title: Mouse prefrontal dopamine transients during cue-action-outcome association learning

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Abstract: As a neurotransmitter with extensive neuromodulatory properties, dopamine plays a pivotal role in a wide range of distinct brain functions. Previous studies have shown that midbrain dopamine neurons projecting to the medial prefrontal cortex (mPFC) contribute to high-level cognitive processes such as cognition, motivation and reward. Phasic dopamine transients encode a reward prediction error (RPE), the difference between predicted and actual outcomes. RPE is a canonical learning signal, and converging evidence suggests that the mPFC may play a role in reinforcement learning. However, the neuronal mechanisms governing this process remain elusive. Here, we examined the time course of dopaminergic transients in mouse mPFC (prelimbic area) during abstract associative learning to study how prefrontal dopaminergic signatures evolve with increasing task competency. We trained mice (n = 10) on an auditory decision-making task with rules switches, requiring the animals to associate auditory cues with directed motor responses (licks) to obtain liquid rewards. Auditory stimuli varied along the dimensions of location and frequency. Only one feature dimension was relevant at a given time, depending on the currently applied rule. After acquiring an initial association, the reward contingencies were changed in the sense of extra- and intra-dimensional shifts. The fluorescent dopamine sensor GRAB DA3h, virally expressed in the mPFC dopaminergic population, allowed us to perform specific, sensitive and temporally highly resolved measurements of dopaminergic signals with fiber photometry over the course of several months while the animals learned the different tasks. Dopamine responses during cue presentation and reward consumption varied with the animals' level of task proficiency. Dopaminergic transients triggered by liquid rewards (correct trials) were largest in novice animals and decreased as the animals became experts. This effect was strongest for the first task rule. In contrast, error trials did not elicit a comparable dopaminergic response, but showed consistently lower dopamine peaks. This pattern suggests that prefrontal dopamine plays a crucial role in modifying behavior based on feedback, supporting its role in reinforcement learning. We are currently also investigating dopamine signaling in orbitofrontal cortex (OFC). This region has been implicated in reversal learning, a prominent feauture of our task. We hypothesize that dopaminergic signalling in OFC may be particularly prominent following unexpected outcomes after rule switches, as a means to facilitate learning.

Disclosures: B. Righetti: None. **T.W. Bernklau:** None. **S.N. Jacob:** None.

Poster

PSTR136: Prefrontal Mechanisms of Learning and Memory

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Topic: H.03. Decision Making

Support: NIH Grant U19NS104648
NIH Grant T32MH065214

Title: The emergence of task representations within the medial prefrontal cortex during associative and reversal learning

Authors: *J. KAMINSKY[1], J. B. JULIAN[2], M. SCHOTTDORF[3], J. YANAR[1], D. W. TANK[3], C. D. BRODY[4];
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Abstract: Making decisions in a complex world requires learning associations and flexibly combining them in goal-oriented ways. Recent theoretical results in artificial recurrent networks, as well as a long history of psychological studies in humans, suggest that the combinatorial usage of such associations is a powerful learning tool. However, it is unclear how this capacity is implemented in the brain. The medial prefrontal cortex (mPFC) has long been thought to maintain representations of learned associations, particularly in tasks that involve shifting between different rules, a process that involves ongoing inference. We seek to test the hypothesis that de novo task learning involves repurposing pre-existing coding schemes within the mPFC. We developed a virtual-reality perceptual discrimination task in which mice learn to associate a continuum of sinusoidal visual gratings with a binary decision. Importantly, our training procedure is designed such that the components of learning, including motor learning, associative learning, memory maintenance, stimulus generalization, and reversal learning, are dissociable across sessions. We recorded unilaterally from mPFC using chronically implanted neuropixel 2.0 probes longitudinally across 1-2 months as mice learned and reversed the stimulus-response contingencies, obtaining stable yields of hundreds of units per mouse each day. We observed the emergence of visual stimulus representations days before mice show evidence of having learned to associate the visual stimulus with particular choice rules, notably earlier than prior reports. Manifold inference and decoding analyses revealed a shift in the mapping of task variables onto a low-dimensional neural scaffold during associative learning. Ongoing work is investigating whether latent dynamical systems models can characterize the emergence of these coding schemes across each stage of learning.

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Poster

PSTR137: Hippocampal Circuits I

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Program #/Poster #: PSTR137.02/L33

Topic: H.08. Learning and Memory

Support: DFG HE 9600/2-1

Title: Soma and dendrite-inhibitory interneurons perform distinct input-output transformations and circuit level operations in hippocampal CA3 and dentate gyrus

Authors: E. HEYNOLD[1], *T. HAINMUELLER[2], G. BUZSAKI[3];
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Abstract: The hippocampus is essential for the storage and recall of declarative memories. It comprises several different anatomical subfields that are connected predominantly in a feed-forward loop starting with the dentate gyrus and progressing through the CA2/3 and 1 areas. Each of these subregions makes unique contributions to hippocampal circuit- and memory-related functions (Buzsaki 1989, Neuroscience, Hainmueller and Bartos, 2020, Nat. Rev Neurosci.). In addition to the specialized principal cells in the respective hippocampal subfields, different types of GABAergic interneurons regulate and coordinate hippocampal networks (Roux and Buzsaki, 2015, Neuropharmacology). While a solid body of work has described activities and functions of interneurons in hippocampal CA1, less is known about potentially unique roles of inhibitory circuits in 'deeper' hippocampal subfields such as CA3 or the dentate gyrus which are the first to process new input from the entorhinal cortex.
Here we aim to close this gap by selective optogenetic labeling and manipulations of different genetically defined subpopulations of interneurons in CA3 and the dentate gyrus. We describe their intrinsic and behavior-related firing characteristics, as well as their responses to salient hippocampal activity patterns. We further investigate the structure of their intra- and extrahippocampal synaptic recruitment and its transformation into their output firing patterns. Using bidirectional optogenetic manipulations, we characterize their impact on postsynaptic targets in the surrounding network. Our results indicate distinct and subfield-specific roles for parvalbumin and somatostatin interneurons in regulating population activity motives, by which they may differentially contribute to the cognitive operations in the respective networks.

Disclosures: E. Heynold: None. **T. Hainmueller:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.03/L34

Topic: H.08. Learning and Memory

Title: Encoding orientation, spacing and direction of 11 different rooms with single Place cell

Authors: *A. AGGARWAL;
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Abstract: Encoding orientation, spacing and direction of 11 different rooms with single Place cell
Hypothesis: Each place cell is connected to several simultaneously active grid cells with varying phases and orientations but single spatial firing frequency.
Methods: To test this, we took place cell firing data from the Moser lab [1] of 342 different place cells from 8 animals in 11 different rooms. Only 2 of the cells in distal most part of the CA3 fired in all the 11 rooms. We took recordings from one of these cells. In MATLAB, we created grid cell firing patterns with spatial firing frequency of 28, 39 and50 cm, 60 different orientations (0-60 degrees) and 25 different phases (5 in the x and 5 in the y-direction) based on[2]. Connection weights between grid and place cells were randomly assigned between 0 and 1 and then trained with backpropagation algorithm to learn place cell firing patterns obtained from the lab data. In the first experiment, grid cells of single frequency, phase (corresponding to door of the room) and all 60 directions were connected to the place cell. In the second experiment, grid cells with 3 frequencies, 2 phases and 60 directions were connected to the place cell.
Results: In the first experiment, place cell firing with smaller fields could be learned but not the ones with larger fields. In the second experiment, firing patterns in all the rooms could be learned. Weights learned were normally distributed between -10 to 15. The spread of weights is wider for rooms with uneven (-10 to 15), larger or multiple firing fields (-7 to 14). While for the rooms with smaller firing fields, the weights are between -2 to 5, And those with medium sized fields, between -5 to 10. For small and medium firing fields, the weights are skewed slightly towards excitatory rather than inhibitory. Larger and multiple firing fields are associated with multi-modal distribution of weights. Weights did not differ a lot on 100 learning trials.
Conclusion: We conclude that our hypothesis was not true as grid cells with multiple spatial frequencies are connected to a place cell. It seems that only a subset of grid cells is active in a room. So, grid cells (and not place cells) resolve the space into spatial distance, orientation, and phase offset. Unique firing patterns of the place cells codify each room with this information.
References 1. Alme et. al., 2014, “Place cells in the hippocampus: Eleven maps for eleven rooms”, PNAS:111(52), 18428-18435. 2. Lian, Burkitt, 2021, “Learning an Efficient Hippocampal Place Map from Entorhinal Inputs Using Non-Negative SparseCoding”, eNeuro, 8 (4) ENEURO.0557-20.2021.

Disclosures: A. Aggarwal: None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.04/L35

Topic: H.08. Learning and Memory

Support: DFG Walter Benjamin fellowship (grant no. MA 10301/1-1, A.M)
FACES Pilot Research Award, NYU (A.M.)

Title: Relationship of hippocampal sharp-wave-ripples and interictal epileptiform discharges in an Alzheimer's Disease mouse model: 1024-channel recordings from the entire hippocampus

Authors: *A. MASLAROVA, M. VOROSLAKOS, D. AYKAN, G. BUZSAKI;
New York Univ., Neurosci. Inst., New York, NY

Abstract: Interictal epileptiform discharges (IEDs) are associated with memory dysfunction in epilepsy and Alzheimer's Disease (AD). IEDs occur preferably during sleep and potentially disrupt memory consolidation by interfering with hippocampal sharp-wave-ripples (SWRs) - brief oscillations crucial for episodic memory. However, the mechanism is not clear. In the CA1 area, IEDs and SWRs show overlapping current sinks and sources as well as brain state-dependence, suggesting that they might share a common generation mechanism. This complicates selective pharmacological suppression of IEDs without affecting SWRs. To explore this relationship, we characterized hippocampus-wide propagation and neuronal modulation of IEDs and SWRs in an AD mouse model. **Methods:** We obtained high-density recordings from the entire dorsal hippocampus (1024 channel SiNAPS probes, Neuronexus) of adult transgenic head-fixed mice (APP/PS1). We assigned recoding channels as well as isolated and identified neurons to the main hippocampal subfields: dentate gyrus (DG), CA3, CA2 and CA1 and computed neuronal firing modulation by subfield. Using current-source-density (CSD) analysis, we identified the origin and described the propagation pattern of SWRs and IEDs throughout the hippocampus. **Results:** Consistent with previous rodent studies, SWRs displayed a narrow-band (~140-200 Hz) frequency increase confined to CA1/CA2, even though they were associated with a brief (~100 ms) positive/negative neuronal modulation in all subfields. IEDs were characterized by high-amplitude (~0.4 mV-3 mV) local field potential changes throughout the hippocampus and neighboring regions and a broadband frequency increase (~20-300 Hz). CSD analysis revealed an early current sink in the DG molecular layer for most IEDs. However, a subset of IEDs started in CA3. Bilateral recordings showed that the latter events likely propagated from the contralateral hippocampus. IEDs were followed by global inhibition of neuronal firing (up to 500 ms) which was most prominent in interneurons. **Conclusion:** Our findings demonstrate that in the hippocampus, IEDs are initiated in the DG-CA3 and propagate along the trisynaptic pathway to reach CA1, resulting in overlapping spectral properties and current sinks and sources with SWRs in CA1. The suppression of neuronal firing post-IEDs suggests a transient disruption of global hippocampal rhythms, potentially accounting for SWR-suppression after IEDs. The largely overlapping mechanism and anatomical substrates of IEDs and SWRs make their selective pharmacological targeting difficult. Other solutions, such as closed-loop interventions are, therefore, warranted.

Disclosures: A. Maslarova: None. **M. Voroslakos:** None. **D. Aykan:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.05/L36

Topic: H.08. Learning and Memory

Support: Simons Collaboration on the Global Brain Transition to Independence Fellowship
Bodossaki Foundation Scholarship for Postgraduate Studies
Swiss-European Mobility Program for Worldwide Projects and Traineeships
NIH NINDS grant 1RF1NS12712201
NIH grant R01MH122391
NIH grant U19NS107616
NSF grant 1707316

Title: Hippocampal neuronal activity is aligned with action plans

Authors: *I. ZUTSHI[1], A. APOSTOLELLI[2], W. YANG[3], Z. ZHENG[1], T. DOHI[1], E. BALZANI[4], A. H. WILLIAMS[1], C. SAVIN[1], G. BUZSAKI[5];
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Abstract: Neurons in the hippocampus are correlated with different variables including space, time, sensory cues, rewards, and actions, where the extent of tuning depends on ongoing task demands. However, it remains uncertain whether such diverse tuning corresponds to distinct functions within the hippocampal network or if a singular computation can account for these observations. To disentangle the contribution of externally driven cues versus a single internal computation, we developed a task where space, auditory tones, rewards, and context were juxtaposed with changing relevance. High-density electrophysiological recordings were performed from CA1 as mice performed this task. Consistent with previous reports, we found neurons with correlated firing to each modality, including auditory frequencies, reward, space, and context-dependent remapping. Yet, by comparing movement paths across conditions, we observed that external variables had limited direct influence on hippocampal firing. Instead, spiking was influenced by intentional trajectories toward future goals and was further modulated by goal uncertainty. Our results support the view of the hippocampus as an intrinsic sequence generator, with cell assemblies initiated and updated by action plans toward deliberate goals. We propose that the apparent tuning of hippocampal neuronal spiking to different sensory modalities emerges as a consequence of such alignment to the action progression within a task rather than a direct representation of externally driven features.

Disclosures: I. Zutshi: None. **A. Apostolelli:** None. **W. Yang:** None. **Z. Zheng:** None. **T. Dohi:** None. **E. Balzani:** None. **A.H. Williams:** None. **C. Savin:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.06/L37

Topic: H.08. Learning and Memory

Title: Activity dependent perturbation of E-I network connectivity in the hippocampus during development.

Authors: *G. HENZE[1], R. HUSZAR[2], G. BUZSAKI[3];
[1]New York Univ. Langone Hlth., New York, NY; [2]Neurosci. Inst., New York Univ., New York, NY; [3]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: Neural activity is important for the maturation of perisomatic inhibition in developing neural networks. Developmental trajectory of inhibition shapes receptive field tuning in excitatory neurons (Dorrn et al., 2010), and depends on intact sensory inputs in critical early life periods (Modol et al., 2020). At the same time, inhibitory neurons undergo a wave of apoptosis (Southwell et al., 2012) that contributes to the establishment of the E/I ratio. This process is also activity-dependent, in that neural activity of presynaptic excitatory neurons regulates the survival of their local postsynaptic interneurons (Wong et al., 2018). Here, we examined activity-dependent survival of inhibitory neurons in the hippocampus, where excitatory neuron convergence onto local interneurons is biased to presynaptic populations of the same embryonic birthdate (Huszar et al., 2022). We investigate whether excitatory neurons born on the same day and subjected to depolarization or hyperpolarization in early life bring about corresponding changes in connectivity on to local interneurons. We electroporated CA1 progenitors with excitatory and inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) along with Channelrhodopsin-2 (ChR2) at embryonic day 15 (E15). Between postnatal days 5 and 8 (P5-P8), mouse pups received two daily injections of clozapine-N-oxide (CNO) to activate the expressed DREADDs in pyramidal cells to increase or decrease firing rates of same birthdate neurons. Following maturation, animals were implanted in the CA1 with silicon probes coupled with optic fibers. They rested in their homecage throughout each recording, concluded with brief light stimulation to identify birthdated pyramidal neurons. Connectivity between excitatory and inhibitory neurons was inferred based on fine timescale, lagged synchrony in the cross-correlation function (Gerstein and Perkel 1969 ; English et al., 2017). Preliminary data revealed increased convergence onto shared interneurons from same birthdate pyramidal neurons relative to controls. In future work, we expand on these results and investigate the bidirectionality of connectivity change. This experimental paradigm offers a way to both manipulate E/I balance and monitor its consequences in the adult, freely moving animal, which may offer insights into neurodevelopmental disorders.

Disclosures: G. Henze: None. **R. Huszar:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.07/M1

Topic: H.08. Learning and Memory

Title: Developmentally structured coactivity and plasticity in the hippocampal trisynaptic loop

Authors: *R. HUSZAR[1], A. KIRSANOV[1], G. HENZE[2], D. HUILGOL[3], Z. HUANG[4], G. BUZSAKI[5];
[1]New York Univ., New York, NY; [2]New York Univ. Langone Hlth., New York, NY; [3]Duke Univ. Sch. of Med., Durham, NC; [4]Dept. of Neurobio., Duke Univ. Med. Ctr., Durham, NC; [5]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: The hippocampus is a key player in learning and memory. Research into this brain structure has long emphasized its plasticity and flexibility (McClelland et al., 1995), though recent reports have come to appreciate its remarkably stable firing patterns (Mizuseki et al., 2013). How plasticity updates networks without eliminating their preexisting activity patterns remains an open question, largely due to a lack of experimental access points to neural populations with consistent and known connectivity. Development may provide one such access point (Cossart and Khazipov 2022). We show that CA1, CA3 and DG principal neurons of the same embryonic birthdate exhibit prominent cofiring across different brain states. These features are partly explained by structured connectivity between pyramidal cells and local interneurons (Huszar et al., 2022). Prior anatomical work showed that same birthdate excitatory neurons across hippocampal subregions are synaptic partners (Deguchi et al., 2011) with highly clustered connectivity on common dendritic branches (Druckmann et al., 2014). This finding suggests the presence of developmentally installed circuit motifs within and across hippocampal subfields that impose constraints on activity patterns generated in these networks. Here, we explore the consequences of this structured network connectivity on hippocampus-dependent learning. We birthdated populations of CA3 and CA1 neurons with intrauterine virus injection of AAV9-CAG-Cre followed by adult injection of pAAV-EF1a-DIO hChR2 into CA3 and CA1. After recovery, we implanted high-density silicon probes equipped with optic fibers in the right CA1 and CA3. Same birthdate populations were identified with short-pulse optogenetics in each subfield. Animals were trained in a ‘cheeseboard’ spatial memory task that required encoding novel reward locations on each day. To isolate learning-related changes to population activity, we used contrastive dimensionality reduction to isolate a subspace of neural activity that captured reactivated patterns in post-learning sharp wave ripples. These patterns developed with task-progression, signaled proximity to the goal locations, and their reinstatement in probe sessions predicted memory performance. Throughout learning, individual CA1 neurons read out CA3 activity within the learning-related subspace, and birthdated CA1 neurons were best predicted by their same birthdate CA3 peers. Learning-related changes are biased to occur within populations of the same embryonic birthdate, which highlights the functional importance of microcircuits shaped by common developmental history.

Disclosures: R. Huszar: None. **A. Kirsanov:** None. **G. Henze:** None. **D. Huilgol:** None. **Z. Huang:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.08/M2

Topic: H.08. Learning and Memory

Support: SNSF P500PB_214401

Title: Distributed temporal expectation signals across the mouse brain

Authors: *N. NITZAN[1], G. BUZSAKI[2];
[1]New York Univ., New York, NY; [2]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: The survival of the organism in a dynamic environment depends on its ability to guide actions in time. This capacity relies on anticipating upcoming events, a phenomenon known as temporal expectation, often measured by omitting the expected cue. A prominent neuronal pattern that effectively encodes temporal information is ramping, i.e., a gradual increase or decrease in firing rate over time. However, how temporal expectation is represented across distributed brain areas is poorly understood. To this end, we analyzed data from mice performing a visual change detection task in which subjects are shown a series of natural images interspersed by 500 ms gray screen and are rewarded for correctly reporting a *change* in the identity of the image. Occasionally, the regular sequence of stimulus presentations was interrupted by randomly omitting a stimulus, affecting 5% of non-change stimuli. Six Neuropixels probes targeted the various visual cortical areas, as well as multiple thalamic, hippocampal and midbrain areas. By analyzing neuronal firing patterns following stimulus omission, we found that the unexpected disruption of stimulus presentation resulted in a robust ramping of firing rates in selective subpopulations of neurons in all areas. In visual areas, the ramping of neurons during stimulus omission was correlated with their ramping during inter-stimulus intervals, while the majority of non-visual areas responded only during omission. In the visual cortex, most of the omission-sensitive neurons (i.e., ramping up during omission) resided in deep layers and comprised both pyramidal cells and interneurons. The firing rate of cells during stimulus omission was highly predictive of their stimulus-response lags. While the majority of the visual cortex population responded to images, omission-sensitive neurons were suppressed during stimulus presentation. This anti-correlated activity was maintained during spontaneous activity, where the spiking activity of omission-sensitive neurons was suppressed during population bursts. Ramping activity can be generated by top-down inputs or via recurrent network interactions. To disentangle these origins, we detected putative excitatory and inhibitory monosynaptic connections from the cross-correlograms of visual cortex neurons. We found that omission-sensitive neurons were preferentially inhibited by interneurons with negative omission scores, whereas substantially fewer inhibitory connections were detected in the opposite direction. Our findings suggest that temporal expectation signals are distributed across multiple areas and, in the visual cortex, are brought about local mechanisms.

Disclosures: N. Nitzan: None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.09/M3

Topic: H.08. Learning and Memory

Support: NIH Grant R00MH128772

Title: Blind in vivo localization of microelectrode array via functional correlation patterns in hippocampus

Authors: *T. HE[1], A. MASLAROVA[2], M. VOROSLAKOS[2], C. LI[1], Y. LIU[1], G. BUZSAKI[2], E. VAROL[1];
[1]New York Univ., Brooklyn, NY; [2]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: In electrophysiology, precise in vivo localization of recording sites in deep brain structures is crucial for consistent targeting in multi-day recordings and accurate deep brain stimulation. However, current approaches present their own challenges: brain atlas-guided probe insertion may be imprecise due to anatomical variability, CT or MRI scan based localization may lack the spatial resolution for subregion structures, and post hoc histology misses longitudinal information in chronic recordings. Focusing on mouse recordings, we present a learning-based automatic localizer to identify hippocampus sublayers from high-density extracellular recordings. Our framework operates on functional correlations of Local Field Potential between channels and employs latent features in low dimensional manifolds for region identification. Critically, we observe that neural manifolds across sessions and animals share a common geometry, perturbed by simple transformations. To minimize this variability, we align all neural manifolds to a common space using two methods: a linear approach that learns a rotation and translation for each session's manifold, and a nonlinear neural network approach with supervised contrastive learning to map different subject recordings into a shared embedding. Both methods yield embeddings that minimize cross-subject variability while preserving cross-region variability. This enables us to learn a probabilistic decoder to predict regions of each channel from learned embeddings. We demonstrate our method on mice Neuronexus recordings with 1024 channels over 8 shanks, providing a better spatial coverage than linear probes like Neuropixels. Our predictions are consistent with neuroanatomy of the hippocampus, resembling the layered structures without prior modeling. Within 7 animals' recordings, it is able to localize 1024 channels with 93% accuracy using only 5% labeled channels, outperforming the baseline model adopted from LOLCAT (Schneider et al. 2023). Across sessions, our model predicts hippocampal regions with 71% accuracy using minimum supervision in the target session. These results suggest that hippocampal regions are distinguishable by their functional correlations with other brain regions, generalizing across subjects and probe designs.

Disclosures: T. He: None. **A. Maslarova:** None. **M. Voroslakos:** None. **C. Li:** None. **Y. Liu:** None. **G. Buzsaki:** None. **E. Varol:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.10/M4

Topic: H.08. Learning and Memory

Title: Physiological and behavioral correlates across the longitudinal axis of the hippocampal CA1 subregion

Authors: *K. MCCLAIN[1], M. VOROSLAKOS[2], G. BUZSAKI[3];
[1]NYU Neurosci. Inst., New York, NY; [2]NYU, New York, NY; [3]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: The hippocampus (HPC) enables memory consolidation and spatial navigation through wide-spread communication with distal brain regions. Hippocampal signaling is organized along the longitudinal axis of HPC, which segregates distinct topography of long-range projections (*e.g.*, RSC receives projections from dorsal HPC, while PFC receives projections from ventral HPC). Numerous cellular properties have been shown to vary along this axis, including transcriptional profiles, neurogenesis, synaptic-changes, and vascularization. The resulting longitudinal structure of hippocampal activity and its implications for how information is routed to various partner regions is not well understood. A few previous studies have found a longitudinal gradient in place field size or spatial resolution, though the specificity and smoothness of this gradient remains ambiguous. Nonetheless, this gradient of scales has been an important piece of evidence for computational theories of generalization and associative learning in HPC. In this study, we performed simultaneous recordings from multiple locations in CA1 subregion of HPC, ranging from dorsal (dCA1), intermediate (iCA1) to ventral (vCA1) during linear track running in rats. We found that canonical place cells (with compact place fields and theta-phase precession) are primarily located in dCA1. Pyramidal cells in iCA1 often demonstrate precise theta-phase coding of position, but show little firing-rate coding. In vCA1 little phase or rate coding of position is evident. Thus, categorical distinctions between spatial representations in dCA1, iCA1 and vCA1is not a continuum, and no subsegment can accurately be considered a ‘scaling’ of another. Instead, we identified another aspect of the spatial representation that varied with longitude: allo-vs-ego-centricity. Across the two running directions, dCA1 tends to show run direction-specific neuronal sequences (i.e., allocentric representations), while vCA1 neurons show more egocentric representations where spatial tuning is flipped depending on running direction. An approximately linear gradient between these extremes exists across the longitudinal axis.

Disclosures: K. McClain: None. **M. Voroslakos:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.11/M5

Topic: H.08. Learning and Memory

Support: R01 NS113071

Title: Rapid brain state alterations during vocal interaction in the singing mouse (S. teguina)

Authors: *Y. FUJISHIMA[1], C. KEMERE[2], G. BUZSAKI[3], M. A. LONG[1];
[1]Neurosci. Inst., NYU Sch. of Med., New York, NY; [2]Electrical and Computer Engin., Rice Univ., Houston, TX; [3]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: Alston's singing mouse (*Scotinomys teguina*) provides a unique opportunity to address the neural dynamics underlying interactive vocal exchange. In response to a conspecific song, *S. teguina* vocally responds within a few hundred milliseconds to the offset of the conspecific songs ("counter-singing"), resembling the temporal profile inherent in human conversation. However, the probability and timing of vocal responses are highly heterogeneous in *S. teguina*, and our preliminary behavioral results suggest that factors such as the vocal partner's identity and location can affect this process. How the brain integrates these external factors to influence vocal responses remains unclear. Given that spatial and social information is believed to be computed in the hippocampal system, we recorded from the CA1-dentate axis of the dorsal hippocampus with silicon probes in freely moving *S. teguina*. To date, our local field potential (LFP) analysis shows increased theta and particularly gamma power when the animal is attentively listening to a conspecific song (followed by counter-singing). Unexpectedly, we observed that when the mouse begins to sing, theta and gamma power decreased immediately and to a level characteristic of consummatory classes of behavior. These results suggest that *S. teguina* rapidly switches between complementary brain states when engaged in perceiving the "song" of a conspecific and self-vocalization. On the basis of brain state correlations, execution of singing is a species-specific behavior and is more similar to reward consumption or grooming than to voluntary actions. Further experiments and analyses will investigate how the brain encodes relevant information to enable rapid transformation of the brain states and behavior.

Disclosures: Y. Fujishima: None. **C. Kemere:** None. **G. Buzsaki:** None. **M.A. Long:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.12/M6

Topic: H.08. Learning and Memory

Support: Horizon 2020 Marie Sklodowska-Curie grant agreement No 892957.

Title: Brain state-dependent activity patterns of dorsal medial thalamic neurons

Authors: *G. S. KOMLÓSI[1,2], L. ACSADY[1], G. BUZSAKI[3];
[1]HUN-REN Inst. of Exptl. Med., Budapest, Hungary; [2]Neuroscience, New York University, Langone Medical Center, New York, NY; [3]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: The dorsal medial thalamus (dMT) is a group of non-sensory thalamic nuclei that has been implicated in arousal and in the homeostatic maintenance of sleep-wake structure. Neocortical slow oscillations and hippocampal sharp wave ripples are the hallmarks of non-rapid eye-movement (NREM) sleep and reflect synchronous activation of neocortical and hippocampal neuronal ensembles, respectively. The dMT is reciprocally connected to the prelimbic cortex (PL), and to the hippocampus through the ventral subiculum (vSUB) with fast glutamatergic synapses. The connection patterns of the dMT with the two systems differ suggesting heterogenous dMT involvement with hippocampal and cortical network activity. We performed large-scale single unit recordings from dMT neurons during unrestrained sleep-wake behavior, while simultaneously recorded single unit and population activity from the ventral hippocampus/subiculum and the prelimbic cortex, respectively. We used a calretinin-Cre mouse line (CR) since CR neurons are abundant in the dMT and absent from neighboring nuclei. Using Cre-dependent viral tracing we show that the spatial distribution of vSUB-projecting CR-neurons and the distribution of vSUB efferents largely overlap and are confined to the anterior part of the dMT. We identify Channelrhodopsin-2 in CR-dMT neurons by somatic and axonal opto-tagging, and we show that the spatial distribution of vSUB- and PL-projecting CR-dMT neurons matches the connectivity data. In line with the anatomical data, we found that dMT neurons with hippocampal ripple and theta-related activity (both wake and REM) reside mainly in the anterior part of dMT. While spiking activity of the majority of dMT neurons was low during cortical DOWN states in NREM sleep, a subset of them selectively increased its activity. DOWN state active (DSA) neurons located posterior to the vSUB-innervated zone, and their activity was either negatively or not correlated with hippocampal ripples. The spiking activity of DSA neurons negatively correlated with multi-unit activity recorded from the PL both in sleep and wakefulness. Furthermore, while DSA neurons fired in synchrony with each other, their spiking was negatively correlated with non-DSA neurons of dMT both in NREM sleep and during wakefulness. Our results reveal the presence of antagonistic subnetworks within the dMT. These findings demonstrate how neocortical and hippocampal/subicular regions can influence activity in this “limbic” thalamic nucleus.

Disclosures: G.S. Komlósi: None. **L. Acsady:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.13/M7

Topic: H.08. Learning and Memory

Support: U19NS107616

Title: Brain state-dependent neuromodulation

Authors: *M. VOROSLAKOS[1], D. AYKAN[2], G. BUZSAKI[2];
[1]NYU, New York, NY; [2]NYU Grossman Sch. of Med., New York, New York, NY

Abstract: Rationale: Transcranial Electrical Stimulation (TES) is a noninvasive method that can modulate neuronal activity. It is presumed in clinical studies that combining stimulation with a task specific to a brain region, known as 'functional targeting', can improve the specificity of TES. The underlying principle is that neurons in task-specific brain regions are more depolarized due to receiving many simultaneous inputs, making these areas more susceptible to external perturbations. However, it remains unclear how stimulation can provide functionally specific effects to active regions, given that neuronal excitability can change based on behavior, sensory input, and brain state.
Methods: To measure how brain state/network excitability can influence the efficacy of TES, we monitored large-scale single unit activity in response to brain stimulation in retrosplenial cortex (RSC), CA1 and CA3 regions of the hippocampus in mice. We collected data during homecage and open field exploration using a Neuropixel 2.0 probe. As cortical state during wakefulness is tightly coupled to changes in pupil size, we measured the pupil diameter of the same animals in head-fixed condition while they underwent transcranial stimulation. In a separate cohort, we also measured the efficacy of TES and acetylcholine levels using G protein-coupled receptor-activation-based acetylcholine sensor ($GRAB_{ACh}3.0$) with a fiber-photometric fluorescence readout in the hippocampus of freely moving mice.
Results: In our electrophysiology experiments, we found that the average firing rate of pyramidal cells in the hippocampus and cortex is modulated differently by TES during wakefulness, NREM and REM sleep. Simultaneous monitoring of ACh-binding by fiber photometry showed a remarkable match between TES-responsivity (measured by changes in firing rate of single units during 4 sec of TES followed by 4 sec of no stimulation) and ACh levels. Further supporting the role of ACh, we found a strong, linear relationship between TES-responsivity and changes in pupil diameter. This effect was highest in CA1 compared to CA3 and RSC, where the main axis of the neurons was better aligned with the external electric fields.
Conclusions: Our results indicate that ongoing brain state can strongly influence the efficacy of TES. These studies can also lay the groundwork for brain state-dependent targeted treatment of neuropsychiatric diseases, where neuromodulator activity is often altered.

Disclosures: M. Voroslakos: None. **D. Aykan:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.14/M8

Topic: H.08. Learning and Memory

Support: NYU DURF Grant

Title: Neuromodulatory dynamics: unveiling the interplay of acetylcholine and oxytocin in social behaviors

Authors: *X. GU[1], Y. ZHANG[2], G. BUZSAKI[3];
[1]New York Univ., Long Island City, NY; [2]Neurosci., nyu grossman Sch. of Med., NEW YORK, NY; [3]Neurosci., New York Univ., Langone Med. Ctr., New York, NY

Abstract: Theta oscillation is believed to provide a temporal framework for coordinating neural activities across different brain regions, particularly in processes related to learning and memory. Interestingly, distinct types of theta rhythms have been observed during social and non-social encounters, yet the underlying network mechanisms driving these differences remain largely elusive. Neuromodulators are hypothesized to play a crucial role in modulating these various theta oscillations, with acetylcholine (ACh) and oxytocin (OXT) emerging as key players. ACh is known to promote theta oscillations involved in cognitive functions, particularly memory formation, while OXT is implicated in regulating social behaviors such as bonding, trust, and empathy. The intricate interplay between these factors influences the encoding and retrieval of social information, thereby shaping social interactions and relationships. In our prior research, we delved into the dynamic fluctuations of acetylcholine (ACh) and oxytocin (OXT) levels, exploring their correlation with brain oscillations and their interaction within the hippocampus. As we unraveled the contributions of these neuromodulators to brain state regulation, we aimed to bridge the gap between neural data and social behavior. This endeavor required deciphering how neural network activities respond during various behavioral tasks and how neuromodulators affect social states. To achieve this, we developed standardized tools for automatically annotating complex social behaviors in mice. Our goal was to correlate these behaviors with changes in neuromodulator levels and types of theta oscillations. We employed large-scale extracellular electrophysiology recording to capture neural data and dual-color fiber photometry to measure ACh and OXT levels simultaneously. In parallel, we will undertake the training of mice to perform various behavioral tasks, leveraging a deep-learning model to annotate their behaviors from recorded video footage. Our initial results are promising, demonstrating the effectiveness of the model in accurately displaying animal tracks. Moving forward, we want to refine the model to annotate different behaviors across diverse experimental settings and align behavioral data with neural data, specifically neuromodulator signals and brain oscillations. While the methods involved may be complex and interdisciplinary, our approach is rooted in the importance of integrating chemical and behavioral perspectives to understand how species' actions shape neural responses. With the foundations we built in previous research projects, we already have useful data to analyze.

Disclosures: X. Gu: None. **Y. Zhang:** None. **G. Buzsaki:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.15/M9

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

Support: This work was supported by funds from the NINDS IRP

Title: Visualizing the spatiotemporal profile of acetylcholine signaling along individual cholinergic axons within the ventral hippocampus

Authors: *C. ZHONG[1], N. S. DESAI[2], Y. LI[5], D. A. TALMAGE[3], L. W. ROLE[4];
[1]NIH/NINDS, Bethesda, MD; [2]NINDS, Bethesda, MD, ; [4]NINDS, [3]NINDS, Bethesda, MD;
[5]Peking Univ., Beijing, China

Abstract: The cholinergic projections from the medial septum and diagonal band complex (MS/DB) to the ventral hippocampus (vHipp) are engaged in various cognitive processes, including attention, learning and memory. The mechanism and time course of cholinergic signaling in CNS circuits has been the topic of considerable controversy. The classical view is that slow and sustained changes (seconds to minutes) in ambient acetylcholine (ACh) determine cholinergic "tone". More recently there have been reports of more rapid changes in ACh signaling with transient peaks of responses, perhaps reflecting more spatially localized release on a milliseconds timescale. Direct detection of the spatial and temporal profile of endogenous ACh release have is now possible using genetically encoded ACh sensors. To precisely define the spatial and temporal profile of MS/DB cholinergic signaling along the projections within the ventral hippocampus, we labeled cholinergic afferents by expression of a channel rhodopsin variant with pAAV-DIO-hChR2(H134R)-EYFP in MS/DB cholinergic neurons of Chat-Cre mice. To detect ACh release, and we used a recently developed red ACh sensor, GRAB ACh1.7. Optimal optogenetic stimulation parameters (1 HZ, 50 ms x 20) of MS DB axonal projections were defined by as those that elicited consistent "spikes" of sensor response to each light pulses. Each stimulus evoked a rapidly rising (sensor limited to 50 ms), and decaying (200- 300 ms range) signal. We detected sensor signal with narrowing the window of optogenetic stimulation to 3 µm along the axonal process, consistent with release being spatially delimited. Overall these data indicate that ACh release with stimulation of ChR2 expressing cholinergic axons in vHipp is both fast and local. Addition of an AChE inhibitor (ambenomium,10 µM) to the bath and repeat 1 Hz x 20 stimuli, revealed an increase in the inter-spike signal that mounted with each of the first ~10-12 pulses and then decayed back to pre-stimulus baseline. There was no detectable change in rise time of the optogenetic stimulated peaks in the presence of ambenomium. Likewise, there was no detectable increase in sensor signal with the addition of ambenomium, but without optogenetic stimulation. In 10 experiments (5 animals) optogenetic stimulation of a 3-10 µm segment of cholinergic axon at 1 HZ yielded robust sensor responses at approximately 10% of the regions tested, with detectable signal seen only when imaging along axon, consistent with a relatively sparse distribution of fast and focal ACh release sites.

Disclosures: C. Zhong: None. **N.S. Desai:** None. **Y. Li:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.16/M10

Topic: H.08. Learning and Memory

Support: Austrian Science Fund (FWF): PAT4178023
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European Research Council (ERC): No 692692, AdG "GIANTSYN"
NOMIS Fellowship

Title: Network properties for theoretical memory storage in hippocampal CA3

Authors: *A. NAVAS-OLIVE, J. F. WATSON, T. P. VOGELS, P. JONAS;
IST Austria, Klosterneuburg, Austria

Abstract: The brain is the most complex organ in our body, built to allow us to process and store complex information about the world around us. The hippocampus in particular is critical for learning and memory. It contains the largest autoassociative network in the brain, the CA3 recurrent collateral network, which enables high-capacity storage of information. However, despite decades of research, how the remarkable information storage function of the hippocampus emerges remains unknown. Moreover, how optimized circuit properties relate to hippocampal function in different species remains an open question.
Here, we established a Hopfield-type network model to determine the optimal circuit characteristics leading to maximal memory capacity for networks of different sizes. This CA3-like autoassociative memory network model is able to learn neuronal patterns, and to recall them from incomplete or degraded pattern versions by pattern completion (Bennett et al., 1994, Phil. Trans. R. Soc. Lond. B 343, 167; Guzman et al., 2016, Science 353, 1117). To account for different brain sizes, we applied an analytical approximation, which allows us to compute storage capacity for realistic neuronal numbers. To evaluate how distinct network properties optimize memory storage, we studied networks with a fixed number of total synapses ($2\text{-}60\times10^9$) ranging from large sparse (0.1% connectivity) networks to smaller densely connected (10%) ones.
We find that arranging the same number of synapses in a larger more sparsely connected network achieves up to >4-fold higher memory storage capacity. This tendency was observed for any total number of synapses. We confirmed these findings using a Bayesian inference approach (Papamakarios and Murray, 2016, NIPS) that enables model parameters to be varied in an unbiased manner. Together, these results suggest that an evolutionary drive for improved memory capacity would prioritize an expansion of neural number over an increase in network connectivity. These properties are consistent with direct measurements of CA3 circuit architecture and neuronal morphology across species, where connection probability in CA3 lowered from ~4% in mouse (~110 k neurons/hemisphere) to 1.5% for human (~1.8 M) (Watson et al., 2024, bioRxiv).

Disclosures: A. Navas-Olive: None. **J.F. Watson:** None. **T.P. Vogels:** None. **P. Jonas:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.17/M11

Topic: H.08. Learning and Memory

Support: Marie Sklodowska-Curie Actions Individual Fellowship: 101026635
Austrian Science Fund (FWF): PAT 4178023
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Austrian Science Fund (FWF): Z 312-B27, Wittgenstein Award
ERC AdG: No 692692 "GIANTSYN"
NOMIS Fellowship

Title: Human hippocampal CA3 uses specific functional connectivity rules for efficient associative memory

Authors: *J. F. WATSON[1], V. V. BARROSO[1], A. NAVAS-OLIVE[1], M. R. TAVAKOLI[1], J. G. DANZL[1], K. ROESSLER[2], P. JONAS[1];
[1]IST Austria, Klosterneuburg, Austria; [2]Med. Univ. Vienna, Vienna, Austria

Abstract: The human brain has remarkable computational power. It generates sophisticated behavioral sequences, stores engrams over an individual's lifetime, and produces higher cognitive functions up to the level of consciousness. However, so little of our neuroscience knowledge has been measured or applied to the human brain, and it remains unknown whether this organ is truly unique, or is a scaled version of the extensively studied rodent brain. To address this fundamental question, we determined the cellular, synaptic, and connectivity rules of the hippocampal CA3 recurrent circuit using multicellular patch clamp-recording. This circuit is the largest autoassociative network in the brain, and plays a key role in memory and higher-order computations such as pattern separation and pattern completion. We studied non-sclerotic tissue from temporal lobe epilepsy patients, allowing the most physiological microcircuit investigation of the human hippocampus possible. We demonstrate that human hippocampal CA3 employs sparse connectivity (1.5%), in stark contrast to neocortical recurrent networks (15%). Connectivity sparsifies from rodents to humans, providing a circuit architecture that maximizes associational power. Unitary synaptic events at human CA3-CA3 synapses showed both distinct species-specific and circuit-dependent properties, with high reliability, unique amplitude precision, and long integration times. Anatomical measurements demonstrate that species scaling from rodents to humans has massively expanded neuronal number (16-fold scaling from mouse to human), far beyond the moderate increase in input number per neuron (2.4-fold scaling from mouse to human). We also identify differential scaling rules between hippocampal pathways from rodents to humans, with a moderate increase in the convergence of CA3 inputs per cell (13.2 k inputs per cell, mouse; 17.5 k inputs per cell, human), but a marked increase in human mossy fiber innervation (50 vs 220 inputs per cell between mice and humans). These effects have the potential to dramatically alter the computational complexity of human hippocampal processing. Together, our results reveal unique rules of connectivity and synaptic signaling in the

human hippocampus, demonstrating the absolute necessity of human brain research and beginning to unravel the remarkable performance of our autoassociative memory circuits.

Disclosures: J.F. Watson: None. **V.V. Barroso:** None. **A. Navas-Olive:** None. **M.R. Tavakoli:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a patent application covering expansion microscopy technology. **J.G. Danzl:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a patent application covering expansion microscopy technology. **K. Roessler:** None. **P. Jonas:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.18/M12

Topic: H.08. Learning and Memory

Support: CIHR
NSERC
Canadian Research Chair program

Title: Long-term dynamics of spatial coding in the subiculum

Authors: *I. INEMA[1], G. ETTER[2], S. WILLIAMS[3];
[1]McGill Univ., Montreal, QC, Canada; [2]Douglas Mental Hlth. Inst., Verdun, QC, Canada; [3]Dept Psychiatry, McGill Univ., Douglas Res. Ctr.,, Montreal, QC, Canada

Abstract: Place cells play a fundamental role in encoding spatial information in the brain, with their representations evolving over days and weeks during repeated exploration of familiar environments, a phenomenon referred to as representational drift. However, the way the brain can maintain the stable representations required for the long-term retention of familiar environments given the representational drift is a subject of many studies. It remains unclear whether the representational drift observed in CA1 is also observed in the subiculum, located one synaptic connection downstream from CA1. The subiculum is known for maintaining a stable firing pattern even across visually and geometrically distinct contexts. In this study, we used calcium imaging to track thousands of subicular cells over several weeks of daily exploration of a familiar environment. Our findings reveal the dynamic nature of spatial coding in the subiculum, with each day exhibiting a unique yet proportionally stable set of active cells. To validate the stability of subicular representations across sessions, we developed an unsupervised model designed to efficiently decode position from low-dimensional embeddings of neural activity. We find that subicular representations do not undergo significant remapping in different contexts but also shed light on the intricate interplay of navigational information within subicular cells. Employing an unbiased statistical approach, we uncover a high degree of conjunctive

coding in subicular cells, consistent with previous findings. Moreover, we identify a dynamic code for space within these cells, allowing for the simultaneous maintenance of a stable spatial representation and a degree of variability in the conjunctive code over time. Importantly, our observations challenge the notion of homogeneous drift within the subiculum, revealing that long-term dynamics are shaped by the representational content. To explore the extent of population drift within the subiculum, we employ an unsupervised model to decode position across time, contributing to a comprehensive understanding of long-term spatial coding dynamics within this brain region. This data advances our comprehension of spatial coding in the subiculum over extended periods, highlighting the unique interplay of stable and dynamic representations in maintaining spatial memory.

Disclosures: I. Inema: None. **G. Etter:** None. **S. Williams:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.19/M13

Topic: H.08. Learning and Memory

Support: CIHR
NSERC
Canadian Research Chair program

Title: Unraveling Novel Pathways: Mapping Inputs to CA1 O-LM Interneurons in hippocampus of Chrna2-Cre Mice.

Authors: *F. MANSEAU[1], S. WILLIAMS[2];
[1]Neurosci., Douglas Mental Hlth. Univ. Inst., McGill, 6875 Lasalle blvd, Verdun, Quebec,, Verdun, QC, Canada; [2]Dept Psychiatry, McGill Univ., Douglas Res. Ctr.,, Montreal, QC, Canada

Abstract: OLM Interneurons, situated in the Oriens layer and projecting long axonal extensions towards the apical dendrites of principal cells in the stratum lacunosum moleculare of CA1, are theorized to function as a gateway controlling the retrieval of sensory information and pre-existing memory associations within the hippocampus. The mechanisms underlying the activation of these cells remain elusive. One important missing piece of evidence is the identity of the input to OLM interneurons. Although it is widely recognized that these cells receive extensive input from the medial septum and excitatory recurrent collaterals from local principal cells, it remains incompletely known what other input they receive. Our study employs tracing experiments in Chrna2-Cre mice, utilizing the viral EnvA receptor/rabies virus (TVA/RABV) system adapted from Wickersham et al. (2007) to trace monosynaptic connections from Cre+ starter cells to their presynaptic partners. Leveraging the input connectivity strength index (CSI) method adapted from Ye and Xu (2022), we quantitatively compare input strengths from diverse brain regions onto OLM interneurons in the CA1 region. Our preliminary analysis reveals the

distribution of RABV+ cells primarily in anticipated brain areas such as the medial septum (MS) and hippocampus (HP). Intriguingly, we also detect neuronal inputs in unexpected regions, including the entorhinal cortex (EC), thalamus (TH), locus coeruleus (LC), and select raphe nuclei. These unexpected findings unveil previously undisclosed neural pathways, potentially pivotal for comprehending the regulation of hippocampal OLM interneuron activity. Confirmation of these pathways promises profound insights into broader brain circuitry and its functional implications into principal cell encoding, recall and navigation. Additionally, we are presently investigating the molecular and cellular identity of the projection cells from selected areas.

Disclosures: F. Manseau: None. **S. Williams:** None.

Poster

PSTR137: Hippocampal Circuits I

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.20/M14

Topic: H.08. Learning and Memory

Support: CIHR-191680
CIHR-FDN-148478
Canada Research Chair
Health Brains Healthy Lives
AARF-22-928742
Brain Canada

Title: Structured and unstructured ensembles during REM sleep are modulated by novel and anxiogenic experiences

Authors: J. CHOI[1], J. E. CARMICHAEL[2], G. ETTER[3], ***S. WILLIAMS**[4];
[1]Integrated Program in Neurosci., McGill Univ., Verdun, QC, Canada; [2]Psychiatry, McGill Univ., Westmount, QC, Canada; [3]Psychiatry, Douglas Mental Hlth. Inst., Verdun, QC, Canada; [4]Psychiatry, McGill Univ., Douglas Res. Ctr.,, Montreal, QC, Canada

Abstract: A striking feature of sleep is the existence of two distinct stages conserved across mammalian species. A large body of evidence suggests that non-rapid eye movement (nREM) sleep plays a causal role in consolidating memory by replaying awake experiences. On the other hand, the exact role of rapid eye movement (REM) sleep in memory consolidation remains unclear. While intact REM sleep is integral for the consolidation of awake experience, the neural activity that gives rise to consolidation is unclear. Here, we evaluate whether awake experience is reactivated or replayed by hippocampal CA1 pyramidal neurons during REM sleep using complementary analytical approaches. We find that representations of awake exploration are recapitulated during subsequent REM episodes with varying levels of temporal structure. Specifically, we find that temporally structured sequences are modulated by novel and anxious

experiences. Altogether, these data suggest that while hippocampal ensembles appear by structural priors, salient experiences lead to increased precision in temporal sequences during subsequent REM sleep, suggesting that unique role for REM sleep in salient-experience consolidation.

Disclosures: J. Choi: None. **J.E. Carmichael:** None. **G. Etter:** None. **S. Williams:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.21/M15

Topic: H.08. Learning and Memory

Support: CIHR
NSERC
Canadian Research chair program

Title: Breakdown of OLM interneurons activity during idiothetic vs allothetic based navigations.

Authors: *L. PENAZZI[1], J.-B. BOTT[2], S. AL-ACHKAR[3], S. WILLIAMS[4];
[1]McGill Univ., Verdun, QC, Canada; [2]McGill Univ., Montreal, Verdun, QC, Canada; [3]McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; [4]Dept Psychiatry, McGill Univ., Douglas Res. Ctr.,, Montreal, QC, Canada

Abstract: Representation of navigational variables varies with cognitive demand, which is in part imposed by environmental cues and the internal state of the animal. The hippocampal CA1 region is a well-recognized center for processing and integrating spatial information into cognitive maps. The CA1 area receives significant inputs from the entorhinal cortex and CA3, which represent two critical networks providing self-motion and spatial information, which are both required for successful navigation, as well as spatial encoding and recall. Oriens Lacunosum Moleculare (O-LM) interneurons are well positioned in the CA1 area to provide control of CA3 and EC inputs, as their activation may facilitate CA3 inputs, while reducing those from the EC. In this study, we used head-mounted miniature microscope (Miniscope) for calcium imaging to determine the activity of genetically defined dCA1 O-LM interneurons in freely behaving mice during various spatial navigation settings. The activity of O-LM interneurons during navigation was determined during spontaneous exploration of novel environments, goal-directed navigation in linear environments and allothetic spatial reference memory tasks that comprised complex multi-path and multi-choice segmented maze. Our results provide new insights on discrepancies of previously published results concerning the speed modulation of O-LM interneurons. In addition, this work provides new evidence for an unsuspected diversity of O-LM recruitment in response to task demands, such as the spatial strategy used by the animal, reward contingencies, and the weights of distal and proximal cues. Importantly, our results suggest that O-LM interneurons do not form rigid functional

subpopulations but instead display flexible activity patterns that can preferentially associate with locomotion, immobility, and contextual cues coding in the same task and across different tasks.

Disclosures: L. Penazzi: None. **J. Bott:** None. **S. Al-Achkar:** None. **S. Williams:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.22/M16

Topic: H.08. Learning and Memory

Support: CIHR
NSERC
Canadian Research Chair program
CONACYT

Title: The role of Oriens-lacunosum moleculare interneurons in hippocampal oscillations and memory consolidation during REM sleep

Authors: *B. CONTRERAS[1], J. E. CARMICHAEL[2], S. WILLIAMS[3];
[1]McGill Univ. Integrated Program in Neurosci., Lasalle, QC, Canada; [2]McGill Univ., Westmount, QC, Canada; [3]Dept Psychiatry, McGill Univ., Douglas Res. Ctr.,, Montreal, QC, Canada

Abstract: Oriens-lacunosum moleculare (OLM) interneurons, a subgroup of somatostatin-positive interneurons, are pivotal modulators of hippocampal network activity, crucially influencing the flow of information. These OLM cells act as gatekeepers, managing the input from the entorhinal cortex (EC) and the Schaffer collateral CA3 input onto CA1 pyramidal neurons. This gating mechanism may help control current sensory stimuli, embodied by fast gamma oscillations (~60-120 Hz) from the EC, and the retrieval of existing memories, supported by slow gamma oscillations (~30-60 Hz) from CA3. Activation of OLM cells may lead to inhibition of the distal dendrites of CA1 pyramidal cells, which weakens EC inputs, hence down-regulating fast gamma activity (Leao et al., 2012). Simultaneously, OLM cells may facilitate the influence of CA3 inputs (slow gamma) by inhibiting interneurons that would otherwise dampen the CA3's contribution. Consequently, it is believed that the aggregate effect of OLM cell activation would tend to favor memory retrieval (slow gamma, CA3) over the processing of immediate sensory inputs (fast gamma, EC). OLM cells exhibit rhythmic bursting behavior that aligns with theta oscillations (~8 Hz), suggesting they may coordinate the intricate balance between theta and gamma oscillations. This interplay, known as phase-amplitude coupling (PAC), may orchestrate the timing of neural activity to optimize information processing. PAC is believed to be vital for encoding and retrieving memories in the hippocampus, anchoring the temporal dynamics of information flow. OLM interneurons, through their regulation of theta and gamma oscillations and probable involvement in theta-gamma coupling, could be instrumental in

modulating hippocampal information processing and memory dynamics.Our project aims to rigorously test the hypothesis that CA1 OLM interneurons play key roles in modulating theta and gamma oscillations, as well as in theta-gamma PAC in mice. We used optogenetic tools to silence CA1 OLM interneurons during electrophysiologically recorded theta in running and REM sleep episodes. We present results showing how OLM interneurons can finely regulate theta and gamma oscillations and their coupling during wake and sleep. Additionally, we provide data on the role of OLM interneurons in memory consolidation during REM sleep using hippocampal memory tasks. Our data provides unique insights into the role of OLM interneurons in network activity and in memory consolidation in hippocampus.

Disclosures: B. Contreras: None. **J.E. Carmichael:** None. **S. Williams:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.23/M17

Topic: H.08. Learning and Memory

Support: FR-21-1501

Title: Research on the Impact of High-Intensity White Noise on Rat Behavior and Hippocampal Cell Morphology

Authors: *N. POCHKHIDZE[1,2];
[1]Cell. Neurosci.; Lab. of Brain of Ultrastructure and Nanoarchitechtonics, Ilia State Univ., Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]Laboratory of Brain of Ultrastructure and Nanoarchitechtonics, Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia

Abstract: RESEARCH ON THE IMPACT OF HIGH-INTENSITY WHITE NOISE ON RAT BEHAVIOR AND HIPPOCAMPAL CELL MORPHOLOGY
[1,2] Nino Pochkhidze*, [1,2]Mzia Zhvania, [2]Nadezhda Japaridze, [1] Ilia State University, [2] Ivane Beritashvili Center of Experimental Biomedicine
Exposure of developing rats to high-intensity white noise has shown to induce hippocampal-related behavioral alterations. Previous studies have shown that necrosis and apoptosis of neurons occur when the body is subjected to physical, chemical, or severe pathological stimulation. For this reason, we consider that the long-term noise stress in rats resulted in lesions in hippocampus neurons and synapses of hippocampus.To study the physiological effects of HIWN exposure on organisms, rats were exposed in soundproof chambers to previously recorded HIWN-related noise for 1 hour, either once or for 40 days. As a comparison, unexposed control rats were also used. Rat behaviors were observed through an (1) open field test. (2) The morphologies of neurons and synapses in the hippocampus were also examined by transmission electron microscopy (TEM).(1)Our results indicated that wistar rats of experiment group exposed

to HIWN of 100 dB had significantly lower line crossing number ($P < 0.05$) and significantly longer center area duration ($P < 0.05$) compared with that of control group. (2)After 40 days of HIWN exposure, rearings (the number of times the animal stands on its hind legs) were higher than those of the control group ($P < 0.05$). (3)It was determined that the neuron and synapsis of the hippocampus of the experiment group exposed to 100 dB for 40 d showed signs of damage. First-line indent hipocamus areas are closely related to perception and memory. Therefore, when neurons of the hipocamus are damaged, a variety of mental disorders are likely to occur, such as cognitive decline, memory reduction, or subjective emotional instability. When synaptic morphology changes, the related functions of the brain and CNS change accordingly, further leading to changes in behavior. In conclusion, rats exposed to chronic HIWN have behavioral changes as well as alterations in the morphology of their hippocampal cells.
This research was supported by Shota Rustaveli National Science Foundation of Georgia under award number FR-21-1501

Disclosures: N. Pochkhidze: None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.24/M18

Topic: H.08. Learning and Memory

Support: FG24932

Title: Monosynaptic rabies viral tracing of brain-wide synaptic inputs to dentate gyrus-projecting layer II entorhinal cortex neurons

Authors: *Q. YE[1], G. GAST[2], H. HUYNH[2], Y. TIAN[3], C. LEE[2], X. XU[4];
[1]UC Irvine, Irvine, CA; [2]Univ. of California Irvine, Irvine, CA; [3]Univ. of California, Irvine, Irvine, CA; [4]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: The entorhinal cortex (EC) is a brain region that plays a crucial role in learning and memory. It is considered a gateway connecting the neocortex and the hippocampus. The projections of layer II of EC neurons form the perforant pathway; the EC sends excitatory projections to the dentate gyrus (DG) through the perforant pathway. As the local and long-range circuit connectivity of specific EC neuron types is still understudied, in the present study we leverage recent progress in neural circuit mapping to comprehensively map synaptic circuit inputs to DG-projecting layer II EC neurons. We first injected rAAV2-retro expressing Flpo in the DG of Sim1-Cre mice that express Cre-recombinase mostly in layer II cells in the entorhinal cortex, to label DG-projecting layer II EC neurons with both Cre and Flpo. Then these neurons were targeted by dual Cre and FlpO-dependent AAV expression by injecting helper AAVs (a mixture of AAV8-Ef1a-Con/Fon-oG and AAV8-Con/Fon-TVA-mCherry); their inputs were mapped by a follow-up injection of EnvA-pseudotyped G-deleted rabies virus (RV). We were

able to map the anatomical connectomes of DG-projecting layer II EC neurons using the intersectional viral-genetic approach. Our preliminary results from six mice show that the presynaptic inputs of DG-projecting EC neurons are extensive and come from the brain regions including the olfactory bulb, piriform cortex, CA1, post subiculum, prosubiculum, lateral EC, medial EC, visual cortex, auditory cortex, and temporal association cortex. Our work provides new insights into EC neural circuit organization and function.

Disclosures: Q. Ye: None. **G. Gast:** None. **H. Huynh:** None. **Y. Tian:** None. **C. Lee:** None. **X. Xu:** None.

Poster

PSTR137: Hippocampal Circuits I

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Program #/Poster #: PSTR137.25/M19

Topic: H.08. Learning and Memory

Support: MSIT grant 2021R1A2C1009454
NRF grant 2021R1A6A3A13039751

Title: Anatomical topology of extrahippocampal projections from dorsoventral CA pyramidal neurons.

Authors: *J. LEE, Y.-S. OH;
Brain sciences, DGIST, Daegu, Korea, Republic of

Abstract: The hippocampus primarily functions through a canonical trisynaptic circuit, comprised of dentate granule cells and CA1-CA3 pyramidal neurons (PNs), which exhibit significant heterogeneity along the dorsoventral axis. Among these, CA PNs are known to project beyond the hippocampus into various limbic areas, critically influencing cognitive and affective behaviors. Despite accumulating evidence of these extrahippocampal projections, the specific topological patterns—particularly variations among CA PN subtypes and between their dorsal and ventral subpopulations within each subtype—remain to be fully elucidated. In this study, we utilized cell type-specific Cre mice injected with fluorescent protein-expressing AAVs to label each CA PN subtype distinctly. This method further enabled the dual-fluorescence labeling of dorsal and ventral subpopulations using EGFP and tdTomato, respectively, allowing a comprehensive comparison of their axonal projections in an animal. Our findings demonstrate that CA1 PNs predominantly form unilateral projections to the frontal cortex, amygdala, nucleus accumbens, and lateral septum (LS), unlike CA2 and CA3 PNs making bilateral innervation to the LS only. Moreover, the innervation patterns especially within LS subfields differ according to the CA PN subtype and their location along the dorsoventral axis of the hippocampus. This detailed topographical mapping provides the neuroanatomical basis of the underlying functional distinctions among CA PN subtypes.

Disclosures: J. Lee: None. **Y. Oh:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.26/M20

Topic: H.10. Human Learning and Cognition

Title: Exploring Adult Hippocampal Neurogenesis in the Common Marmoset: Implications for Understanding Species-Specific Differences and Translational Neurobiology

Authors: *S. ENRIGHT[1], S. L. PARYLAK[2], F. H. GAGE[3], J. C. MARTINEZ-TRUJILLO[4]; [1]Univ. of Western Ontario, London, ON, Canada; [2]Salk Inst., La Jolla, CA, ; [3]Salk Inst. for Biol. Studies, La Jolla, CA, ; [4]Schulich Sch. of Med. and Dentistry, Western Inst. for Neuroscience, Western Univ., London, ON.

Abstract: Adult hippocampal neurogenesis (AHN) has been extensively reported in rodents with several studies documenting the developmental and maturation processes of adult-born cells. In mammals, AHN is situated in the dentate gyrus (DG) and has been implicated in learning, memory, and other hippocampal-specific processes. However, studies have reported that AHN seems to occur at lower levels in humans and neurogenic rates are widely disputed. Further research analyzing AHN in non-human primate (NHP) models is necessary to better understand species-specific differences and translate this knowledge to humans. Here, we use dual labelling with bromodeoxyuridine (BrdU) and ethynyl deoxyuridine (EdU) to quantify AHN and the migratory rates of adult-born neurons in a small primate, the common marmosets. Our results show several adult-born neurons within the subgranular zone (SGZ) and mid-granular zone of the DG. These cells express neuronal markers and differ from proliferating glial cells, demonstrating distinct AHN in the adult marmoset. AHN rates seem slower than that in the mouse suggesting differences in AHN are likely related to the species lifespan (15 years in marmosets vs 2 years in mice). We also explore novel methods to examine morphological distinctions between adult-born neurons of NHPs and rodents and the resulting impacts on circuits and behaviour. We propose that the common marmoset may serve as an important intermediate model to translate data from rodent models to human studies to provide insight into neuropsychiatric and neurodegenerative disorders that affect AHN and memory.

Disclosures: S. Enright: None. **S.L. Parylak:** None. **F.H. Gage:** None. **J.C. Martinez-Trujillo:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.27/M22

Topic: H.09. Spatial Navigation

Support: T32NS043126
R01NS101108
I01RX003498

Title: Characterization of hippocampal neuronal and oscillatory activity in freely moving swine using high-density laminar electrodes

Authors: *E. MIRZAKHALILI[1], A. V. ULYANOVA[2], C. D. ADAM[2], H.-C. I. CHEN[2], V. E. JOHNSON[2], J. A. WOLF[2];
[2]Neurosurg., [1]Univ. of Pennsylvania, Philadelphia, PA

Abstract: The hippocampus is integral to learning and memory, and deficits in cognitive function can be linked to its dysfunction. Much of our knowledge about the electrophysiological characteristics of the hippocampus result from years of rodent studies. However, rodents are sub-optimal translational models for many diseases/disorders due to their lissencephalic brain structure. Non-human primates (NHPs) are excellent translational models, but their use is limited due to constraints including ethical concerns. Swine models have the potential to bridge the gap between rodent and human electrophysiological studies without the use of NHPs. In this study, we performed chronic electrophysiological recordings from the hippocampus of male Yucatan miniature swine (n= 8). Using novel wireless technology and multichannel silicon laminar probes (32-128 channels), we continuously recorded from the hippocampus of all animals for over 18 hours per day over several months in their home cage. Additionally, we recorded from some of the animals when they performed behavioral tasks including running in a square maze and performing complex memory tasks using touchscreens. These recordings allowed us to characterize porcine hippocampal electrophysiology, including single unit activity and local field potentials. We observed results that were consistent with those reported in rodents and NHPs. Particularly, for the first time, we showed the presence of place cells in the porcine hippocampus in various environments and tasks. Moreover, during the memory tasks, we detected single units that were active only before and/or after decision making while some other single units were only active during the decision making process. Regarding local field potentials, we detected theta oscillations during locomotion, but they were slower (5-6 Hz) compared to what is reported in rodents (7-8 Hz), but faster than those in humans (4 Hz). Theta oscillations were also strongly present during what appeared to be REM sleep, while the cortex was desynchronized. We observed sharp-wave ripple oscillations when animals were immobile or in slow-wave sleep, but the frequencies of ripples were again slower (~100 Hz) compared to what observed in rodents (~180 Hz). We were also able to detect local field potential interaction across frequencies such as theta-gamma phase amplitude coupling, which are known to play a crucial role in memory tasks. Together, these results highlight the similarities and differences across species, and demonstrate that the technology now exists for swine to play an important role as a translational model while examining the central role of the hippocampus in cognitive functions.

Disclosures: E. Mirzakhalili: None. **A.V. Ulyanova:** None. **C.D. Adam:** None. **H.I. Chen:** None. **V.E. Johnson:** None. **J.A. Wolf:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.28/M23

Topic: H.10. Human Learning and Cognition

Support: NIEHS T32 ES033955
Wallace Coulter Foundation
Canadian Institutes for Health Research (CIHR)
Western Chair in Autism

Title: Sharp wave ripples from the marmoset hippocampus during a freely moving navigation task: analyzing event features, phase-amplitude coupling, and spiking activity

Authors: *C. OTERO[1], D. B. PIZA[2], J. C. MARTINEZ-TRUJILLO[3], J. J. RIERA[1];
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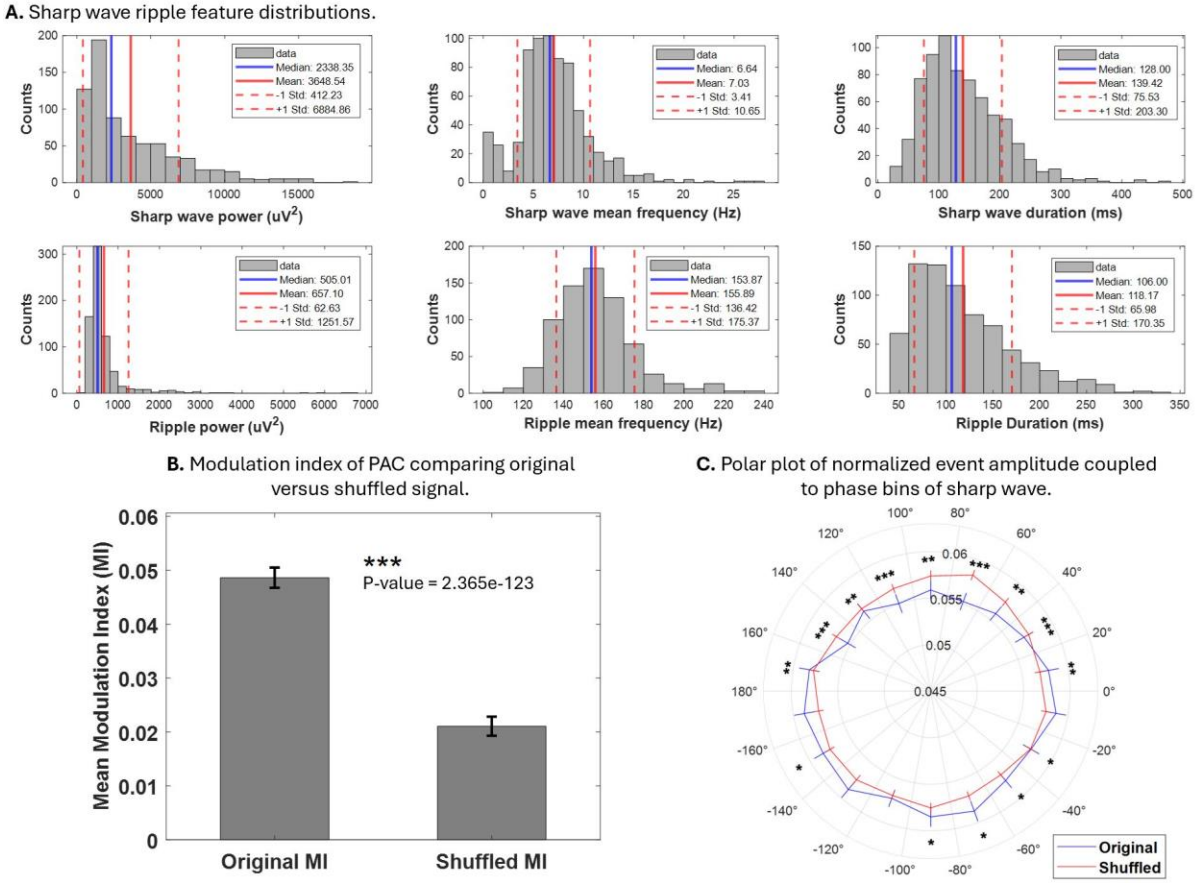
Abstract: Sharp wave ripples (SWRs) are neurophysiological events in hippocampus (HPC) characterized by the co-occurrence of a low-frequency sharp wave (SW) and several high-frequency oscillations (ripple). SWRs result from synchronized neural firing in the Cornu Ammonis (CA) regions of HPC and have been linked to memory encoding and consolidation. Most studies of SWRs have been conducted in rodent and the few studies in primates have been conducted in restrained macaques. Here, we investigate the features of SWRs in a freely moving primate, the common marmoset (Callithrix jacchus), during a spatial navigation-foraging task in a 3D maze. Two marmosets (aged 4-6 yo) were implanted with brush array electrodes (Microprobe Inc, MD) in HPC CA1/CA3 regions. They were also implanted with head caps that were tracked using a motion-tracking system (Optitrak, Natural Point, OR). We measure head/body position signals, Local Field Potentials (LFPs) and single unit responses while the animals navigated through the 3D maze foraging for rewards (banana milkshake). For detection our lab developed an algorithm based on techniques discussed in Liu, A.A. et al., 2022 and detected co-occurring SWs (1-10Hz) and ripples (100-250Hz). We then visually inspected events to confirm the SWR identity with a user GUI. We identified 720 SWRs across four experimental sessions. We applied Hilbert transform, computed phase-amplitude coupling (PAC) as done in Tort et al., 2010, and filtered the signal spectrum to extract SWR features. Finally, the broad band signal was spike sorted to detect single unit activity (Buitrago-Piza et al., 2024). The ripple duration and frequency follow those reported in other species (Figure 1. A). PAC showed coupling between SW and ripple (Figure 1. B) and that the ripple amplitude tends to be diminished during the beginning phases of the SW (Figure 1. C). These results demonstrate that SWRs during navigation in the freely moving marmoset show similar features as reported in rodents and other species. Moreover, the PAC between SW and ripples suggests a deterministic relationship between them.

Figure 1. Feature distribution and phase amplitude coupling across sharp wave ripples in freely moving marmoset.



Disclosures: C. Otero: None. **D.B. Piza:** None. **J.C. Martinez-Trujillo:** None. **J.J. Riera:** None.

Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.29/M24

Topic: H.10. Human Learning and Cognition

Support: CIHR

Title: Sharp wave ripples during virtual navigation and associative memory in the human hippocampus

Authors: *N. MORTAZAVI[1], M. KHAKI[2], B. W. CORRIGAN[3], G. GILMORE[4], J. LAU[4], A. SULLER MARTI[4], J. C. MARTINEZ-TRUJILLO[5];
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Abstract: Introduction: Introduction: Sharp Wave-Ripple complexes (SWRs) are transient electrophysiological events thought to originate within the CA1 subfield of the hippocampus that play crucial roles in memory encoding, consolidation, and retrieval. Although SWRs and their relationship to memory have been extensively studied in rodents, human studies are scarcer. Here, we explore the association between hippocampal SWRs during two behavioural tasks in a virtual environment. We hypothesize that SWRs predominantly occur when memory demands increase during a virtual-navigation task. We recorded stereoencephalography (SEEG) signals from epilepsy patients implanted with depth electrodes. An SWR detection algorithm was developed to identify SWRs from hippocampal electrodes under different conditions. The patients were tested in a baseline/resting condition and in a virtual reality (VR) task. During the VR task, subjects navigated a virtual maze (YOY maze) in which the center is a circular arena, and each side is made of a narrow corridor connected to two end arms. In the circular part, the subjects navigate the maze collecting treasure chests (navigation). They travel to one arm of the maze to perform an associative memory task, i.e., travel through the corridor to the arms and depending on the context of the walls (steel or wood), they collect one of two coloured objects positioned in each arm (e.g. if steel must collect red if wood must collect green). A state-space model was utilized to evaluate dynamic learning curves and to compute learning trials for participants who successfully learned the task. We analyzed HPC-CA1 electrodes in **14** patients and detected SWRs. Kruskal-Wallis tests revealed that SWR rates were significantly higher during the VR task than baseline ($p=0.0078$). However, SWR rates were not significantly different before and after the subjects learned the task ($p=0.43$). Finally, SWR rates were higher during the associative memory period than during the navigation period of the VR task. Our findings suggest a significant association between hippocampal SWRs and memory processes, mainly encoding and consolidation, during associative learning. The diminished frequency of SWRs during navigation tasks supports the notion that SWRs are less likely to be induced by navigational activities alone.

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Poster

PSTR137: Hippocampal Circuits I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR137.30/M25

Topic: H.08. Learning and Memory

Support: R01-AG070592
R13-NS116995

Title: Harmonized segmentation protocol of the hippocampal head on high-resolution in vivo MRI from the Hippocampal Subfields Group

Authors: *M. A. DALTON[1], R. LA JOIE[2], R. DE FLORES[3], T. A. STEVE[4];
[1]Univ. of Sydney, Sydney, Australia; [2]Univ. of California, San Francisco, California, CA; [3]Inserm U1237, Univ. de Caen Normandie, Caen, France; [4]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Several existing protocols are available to segment human hippocampal subfields on MRI scans, but these protocols vary in how they delineate boundaries for each subfield and even which subfields they include. This variability leads to discrepant findings in the literature and impedes direct interpretation of structural and functional neuroimaging results. The Hippocampal Subfields Group (HSG) is an international organization addressing this issue by developing histologically valid and reliable segmentation protocols for high-resolution T2-weighted 3T MRI. HSG has previously created a segmentation protocol for subfields in the hippocampal body and also a protocol for delineating the hippocampal tail. Compared with the hippocampal body and tail, the hippocampal head displays dynamic shifts in subfield location when moving from its anterior to posterior most extents. This is particularly pronounced in the uncal portion of the hippocampus which displays a high degree of morphological variability across individuals. In addition, detecting the stratum radiatum, lacunosum and moleculare (SLRM) layer, which is critical for identifying boundaries between subfields, can be difficult in the hippocampal head. Here, we describe the development of a protocol for segmenting subfields within the hippocampal head using *in vivo* 3T structural MRI. A working group comprising four experts in MRI investigation of the hippocampus and its subfields first developed boundary rules for the inferior, superior, medial, and lateral borders, and for identifying the anterior-most and posterior-most slices of the hippocampal head. Then, to account for dynamic shifts in morphology when moving from the anterior to posterior hippocampal head, several geometric heuristics were developed that best capture the likely location of subfields along the anterior-posterior axis of the hippocampal head based on a novel histological reference data set labelled by three expert neuroanatomists. The segmentation protocol facilitates delineation of the dentate gyrus/cornu ammonis (CA) 3, CA2, CA1 and subiculum subfields. We will discuss initial feasibility results and give an overview of outcomes from the Delphi procedure, a method for gathering and refining expert opinions through iterative rounds of questionnaires to achieve consensus. The finalized, harmonized protocol will be shared as a manual and an automated segmentation protocol for wide adoption.

Disclosures: M.A. Dalton: None. **R. La Joie:** None. **R. de Flores:** None. **T.A. Steve:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.01/M26

Topic: H.08. Learning and Memory

Support: NSF Graduate Research Fellowship DGE-2139899
NIH grant R00MH122582
NIH grant R01MH130367
NIH grant 4R00MH120343
Sloan Fellowship
Whitehall Research Grant
Klingenstein-Simons Fellowship
Ruth L. Kirschstein National Research Service Award Individual Postdoctoral Fellowship F32MH134673

Title: A hippocampal circuit mechanism to balance memory reactivation during consolidation

Authors: *L. A. KARABA, H. L. ROBINSON, R. E. HARVEY, A. FERNANDEZ-RUIZ, A. OLIVA;
Neurobio. and Behavior, Cornell Univ., Ithaca, NY

Abstract: The hippocampus is a key structure for learning and memory. Memory consolidation involves the synchronous reactivation of cells that have been previously active in recent experience during hippocampal sharp-wave ripples (SWRs) in subsequent sleep. SWR incidence increases after learning tasks and disrupting them impairs memory. How the increased firing rates and coordination of task-related cellular ensembles during SWRs are counterbalanced to preserve network stability is not understood. Here, we report a hippocampal network event with distinct cellular and network properties than SWRs, but which is also modulated by learning. This network pattern is generated by a subset of CA2 pyramidal cells and cholecystokinin (CCK+) expressing basket cells which fire a barrage of action potentials (‘BARR’) during non-REM sleep. Individual CA1 neurons and assemblies that increased their activity during learning were strongly reactivated during SWRs but inhibited during BARRs. Disrupting this process via optogenetic silencing of CCK+ basket cells impaired memory consolidation. Importantly, the increase in reactivation during SWRs restored towards baseline during the sleep, but this trend was abolished when BARRs were silenced. Altogether, our results suggest that a CA2 pyramidal cell - CCK+ basket cell subcircuit generates BARRs, a network pattern that acts as a compensatory mechanism of memory reactivation occurring during SWRs. Optogenetic manipulation experiments show that BARRs are necessary for memory consolidation.

Disclosures: L.A. Karaba: None. **H.L. Robinson:** None. **R.E. Harvey:** None. **A. Fernandez-Ruiz:** None. **A. Oliva:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.02/M27

Topic: H.08. Learning and Memory

Support: NIH grant 4R00MH120343
Sloan Fellowship
Whitehall Research Grant
Klingenstein-Simons Fellowship
NIH grant 4R00MH122582

Title: Hippocampal-cortical memory consolidation occurs at learning timescales

Authors: *R. HARVEY[1], C. LIU[2], Z. ZHAO[1], E. CARBAJAL LEON[1], A. OLIVA[1], A. FERNANDEZ-RUIZ[3];
[1]Cornell Univ., Ithaca, NY; [2]Neurobio. & Behavior, Cornell Univ. Neurobio. and Behavior, Ithaca, NY; [3]Neurobio. and Behavior, Cornell Univ., Ithaca, NY

Abstract: Memory consolidation, the process of transitioning memories from initial encoding to long-term storage, remains a central unsolved problem in neuroscience. To elucidate this phenomenon, we examine the complex interplay between the hippocampus and prefrontal cortex in rats throughout novel learning. An influential model of memory consolidation asserts that memories are initially encoded in the hippocampus and are gradually transferred to the cortex via sharp wave ripples (SWR) for long-term storage. However, direct empirical evidence of this SWR-mediated gradual transfer of memories from the hippocampus to the cortex remains elusive. To investigate this phenomenon, we simultaneously recorded several hundreds of neurons with high-density silicon probes in the hippocampus and prefrontal cortex of rats. To capture the dynamics of these two regions during learning, the implanted animals completed novel spatial learning tasks that took several days to gain proficiency. We then examined place cell, assembly, and sequence dynamics within and across structures during learning and subsequent sleep. Our findings reveal a dynamic progression of memory reactivation during post-task sleep across days. While the hippocampus showed a decline in memory reactivation over time, the prefrontal cortex exhibited progressively heightened reactivation, suggesting a sequential process of memory storage as the animal gains experience in the task. We also analyzed the coordination of population activity across structures during theta and SWR states and the emergence of low-dimensional neural representations of task variables. Further, to explicitly test the hypothesis that memories are transferred to the neocortex during hippocampal SWRs, we employed closed-loop optogenetics to silence prefrontal cortex activity during SWRs during post-task sleep. Remarkably, behavioral task performance significantly deteriorated under such conditions, highlighting the behavioral relevance of hippocampal-to-cortical transfer. These results provide a key insight into understanding the precise temporal dynamics of the hippocampal-cortical dialogue and the behavioral outcomes of disrupting this coordination. Together, this work contributes to a deeper understanding of memory dynamics over time and provides direct experimental evidence for the two-stage model of memory consolidation.

Disclosures: R. Harvey: None. **C. Liu:** None. **Z. Zhao:** None. **E. Carbajal Leon:** None. **A. Oliva:** None. **A. Fernandez-Ruiz:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.03/M28

Topic: H.08. Learning and Memory

Support: NIH grant R00MH122582
NIH grant R01MH130367
NIH grant R00MH120343
NIH grant 1DP2MH136496
Sloan Fellowship
Whitehall Research Grant
Klingenstein-Simons Fellowship
Klarman Postdoctoral Fellowship

Title: Combining pupillometry and close-loop neural manipulations during natural sleep reveals a novel mechanism for memory consolidation

Authors: *H. CHANG, W. TANG, A. M. WULF, T. NYASULU, M. E. WOLF, A. FERNANDEZ-RUIZ, A. OLIVA;
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Abstract: One prominent problem that both biological and artificial neural networks face is the interference between previously stored and newly acquired memories, as it can lead to catastrophic forgetting. Theoretical work has suggested that consolidating multiple memories while minimizing interference can be achieved by randomly interleaving their reactivation. An alternative is that the temporal microstructure of sleep can segregate the reactivation of different types of memories during specific substates. To test these two hypotheses, we developed a novel method that combines pupillometry with high-density electrophysiology and closed-loop optogenetic intervention, enabling real-time pupil tracking and pupil-gated disruption of memory reactivation in naturally sleeping mice. Our online algorithm for pupil tracking showed high accuracy when compared with standard offline methods such as DeepLabCut. We recorded pupil dynamics and the activity of large hippocampal ensembles using silicon probes, while mice performed a spatial learning task and during subsequent sleep. We then combined real-time tracking of pupil diameter and detection of hippocampal sharp-wave ripples (SWRs) to optogenetically disrupt memory reactivation during specific non-REM substates. We found that selective disruption of the subset of SWRs (n=5 mice) occurring during contracted pupil non-REM sleep substates was sufficient to impair memory recall while disrupting a similar fraction of SWRs during dilated pupil substates had no behavioral effect. To test whether this manipulation affected all memories or specifically the most recent ones, we trained mice to find a familiar and a novel rewarded location in the same session. Animals (n=4 mice), showed impairment of, specifically, the recent rewarded location but still remembered the familiar one, after SWR disruption during contracted pupil substates. Hippocampal sequence replay and assembly reactivation of task-related neural patterns matched our behavioral results. Thus, our results suggest that non-REM sleep has a micro-structure that temporally organizes memory consolidation into different substates, which can help protect consolidation of newly acquired memories from its interference with prior memories. Our results suggest that the brain can

multiplex distinct cognitive processes during sleep (e.g., initial memory consolidation and subsequent integration) to facilitate continuous learning without interference.

Disclosures: H. Chang: None. **W. Tang:** None. **A.M. Wulf:** None. **T. Nyasulu:** None. **M.E. Wolf:** None. **A. Fernandez-Ruiz:** None. **A. Oliva:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.04/M29

Topic: H.08. Learning and Memory

Support: Cornell University Mong Neurotech Junior Fellowship

Title: Effects of hippocampal sharp-wave ripples on territorial defense strategies in male house mice

Authors: *C. C. VOGT[1], P. PAUDEL[2], Z. ZHAO[2], C. LIU[3], M. SHEEHAN[2], A. FERNANDEZ-RUIZ[2], A. OLIVA[4];
[1]Neurobio. & Behavior, Cornell Univ., Ithaca, NY; [2]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [3]Neurobio. & Behavior, Cornell Univ. Neurobio. and Behavior, Ithaca, NY; [4]Neurosci. Dept., New York Univ., New York, NY

Abstract: The successful establishment of a territory is a critical determinant of individual fitness across taxa including insects, fish, reptiles, birds, and mammals. Animals employ a combination of cues and social signals to demarcate territorial boundaries, and once established, territory holders will remember and defend these boundaries from competitors for extended periods. However, the neural mechanisms underlying the formation and maintenance of territorial behavior remain poorly understood. Here, we investigated the role of hippocampal sharp-wave ripples (SWRs) - a biomarker for memory consolidation and planning - in shaping male defensive reactions in response to border violations by competitors in house mice. We employ a novel, high resolution 24/7 behavioral tracking system to continuously monitor and characterize the movement and social interactions of male mice in a large-scale outdoor field enclosure as they establish territories and engage in territory defense. By experimentally simulating territorial invasions by male competitors in the field, we examine how male mice strategically adjust their territorial defense strategies in response to border violations. To investigate the causal role of hippocampal SWRs in this ecologically relevant behavior, we monitored neural activity in hippocampus with a wireless closed-loop neural interface and selectively disrupted SWRs during post-invasion sleep. By characterizing SWR associated neural content and its disruption, as well as analyzing the behavioral consequences in free-living rodents, we aim to elucidate the role of internally generated brain patterns important for memory in shaping socially relevant competitive behaviors that play a major role in determining fitness outcomes in many animal species.

Disclosures: C.C. Vogt: None. **P. Paudel:** None. **Z. Zhao:** None. **C. Liu:** None. **M. Sheehan:** None. **A. Fernandez-Ruiz:** None. **A. Oliva:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.05/M30

Topic: H.08. Learning and Memory

Title: Dissecting the neural basis of group social and foraging rodent behavior with a highly configurable, high-density, multi-modal neural logger

Authors: *Z. ZHAO, J. PARK, C. C. VOGT, C. LIU, P. PAUDEL, A. OLIVA, A. FERNANDEZ-RUIZ;
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Abstract: *Investigating the neural circuit mechanisms of complex behaviors requires recording and manipulating the activity of large neuronal ensembles without impeding animal movements and interactions. In addition, to understand how the brain represents complex tasks it is necessary to monitor multimodal sensory inputs and locomotor patterns during unrestrained behavior. In recent years, significant progress has been made in methods to investigate the neural basis of behavior in rodents and other animals. However, current methods still fall short when applied to very large environments, group behaviors or when there is a need to integrate neural recordings, manipulations and multi-modal sensing in a wireless platform. To overcome all these limitations and we employed a multidisciplinary engineering approach to develop* a wireless, multi-modal neural interface. This includes: i) a polymer-based, conformable neural probe for long-term chronic monitoring of neural ensembles ; ii) an engineered light-weight (less than 1.5 grams) wireless neural logger with off-the-shelf electronics; iii) a modular system that can be flexibly customized to include different types of sensors (gyroscope, head-mounted camera, ultrasound microphone) as well as current stimulator for electrical or optical stimulation; and iv) an embedded software enabling highly flexible experiment diagram with wireless programmable active/sleep mode control, high-precision synchronization, and programable real-time signal processor . Our system features a highly configurable front-end, capable of supporting up to 384 channels of neural activity and/or physiologically relevant signals. . An embedded neural signal processor ensures low-latency closed-loop neural intervention upon detection of specific neural of behavioral patterns. We demonstrate the capabilities of this platform applying it to the investigation of the neural circuit mechanisms of group social and foraging behaviors in mice and rats. We found that neural assemblies across hippocampal and cortical regions exhibit mixed selectivity, encoding multiple behavioral and physiological variables. Disrupting assembly activation during network events, such as hippocampal sharp-wave ripples, allowed us to causally link specific patterns of neural activity to behavioral outcomes.

Disclosures: Z. Zhao: A. Employment/Salary (full or part-time):; Cornell University. **J. Park:** None. **C.C. Vogt:** None. **C. Liu:** None. **P. Paudel:** None. **A. Oliva:** A. Employment/Salary (full or part-time):; Cornell University. **A. Fernandez-Ruiz:** A. Employment/Salary (full or part-time):; Cornell University.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.06/M31

Topic: H.08. Learning and Memory

Support: NIH grant 4R00MH120343
New Frontiers Grant
Whitehall Research Grant
425 Klingenstein-Simons Fellowship
NIH grant 4R00MH122582

Title: Hippocampal place cell dynamics during rat foraging behaviors in a semi-natural outdoor environment

Authors: *C. LIU[1], Z. ZHAO[2], A. OLIVA[3], A. FERNANDEZ-RUIZ[2];
[1]Cornell Univ. Neurobio. and Behavior, Ithaca, NY; [2]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [3]Neurobio. and Behavior Dept., Cornell Univ., Ithaca, NY

Abstract: The brain has evolved to support behavioral needs for animal's survival in a highly dynamic and complex world. To understand the underlying brain mechanisms, the neuroscience community leverages well-controlled laboratory settings, while lacking the enriched, multimodal, and dynamic sensory stimuli that exist in natural conditions. This approach has provided key insights into our understanding of, for example, spatial navigation, a cognitive process that relies on the hippocampus. Spatial laboratory tasks often require learning of fixed rules and repetitions of many trials, contrasting with animals' behavior demands in an ever-changing environment, such as the real world. Therefore, it remains uncertain how the physiological mechanisms and brain computations underlying the neural representations of space translate to natural conditions. To investigate this question, we conducted electrophysiological recordings in the hippocampal CA1 region of rats while they engaged in a self-paced foraging task in both an outdoor semi-natural enclosure and an indoor laboratory setting. Using customized wireless data loggers and silicon probes, we compared animal behavior and CA1 electrophysiological properties, including single-cell properties, population dynamics, and oscillatory patterns. Our preliminary findings indicate differences in rat's behavior during spatial navigation and foraging, including locomotion patterns, which act as strong modulators of hippocampal dynamics. These results underscore the importance of considering the ecological validity of experimental conditions when studying brain function and highlight the potential impact of environmental factors on neural processes.

Disclosures: C. Liu: None. **Z. Zhao:** None. **A. Oliva:** None. **A. Fernandez-Ruiz:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

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Program #/Poster #: PSTR138.07/M32

Topic: H.08. Learning and Memory

Support: NIH grant 4R00MH122582
New Frontiers Grant

Title: Social Experiences in Rewilded Mice Living in Outdoor Enclosures Reactivate During Sleep

Authors: *P. PAUDEL, C. C. VOGT, C. LIU, Z. ZHAO, R. E. HARVEY, R. NIRAULA, M. SHEEHAN, A. FERNANDEZ-RUIZ, A. OLIVA;
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Abstract: The representation of location is critical for animals to successfully navigate from one place to another. Research in this area has led to the idea of the hippocampus function as a ‘cognitive map’. Although there have been significant advances in understanding the spatial cognitive map's molecular, cellular, and system mechanisms, most of the studies thus far have been conducted in impoverished laboratory environments that fail to capture the full complexity of real-world experiences, as in naturalistic settings, animals can engage in behaviors such as spontaneous foraging, territorial defense, or social interactions, which are all likely to influence the way that spatial memories are encoded, stored, and retrieved. Field studies enable us to capture these adaptive processes firsthand. In this study, we investigated how the properties of hippocampal brain patterns important for learning and memory are modulated by the changes in the spatial and social organization of a population of male mice living in an outdoor field enclosure with monopolizable resource zones. In this environment, male mice establish a territory, actively survey their social environment, and adapt to notable alterations within it. In parallel to the behavior, we conducted extracellular electrophysiological recordings during the invasion and defense of these territories, as well as during sleep. The incidence of hippocampal sharp-wave ripples (SWRs), highly synchronous network events facilitate the consolidation of recent experiences, was increased for several days during this behavior. ‘Cell assemblies’ (groups of neurons that are frequently coactive forming strong interconnections) showed context specific activity and were differentially reactivated during SWRs in subsequent sleep. Specifically, cell assemblies representing a social experience get strongly reactivated, while cell assemblies representing a non-social experience do not. This suggests that experiences of high relevance for animal behavior are incorporated into memory, while other experiences (less relevant for animal’s natural behavior) are not. These results contribute to our understanding of how environmental factors and social dynamics modulate hippocampal memory processes.

Importantly, it opens the possibility to investigate brain principles in ecologically relevant environments.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

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Title: Sleep micro-structure organizes memory replay

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Abstract: Sleep promotes memory consolidation, which is assumed to rely on the replay of recently encoded memories during hippocampal sharp-wave ripples (SWRs). However, during sleep, both new and prior memories are replayed, and it is unclear how labile new memories are stabilized without interfering with old ones. One solution proposed by canonical theories (*McClelland at al., 1995; Sutton and Barto, 1992*) is to randomly intersperse replay of new and prior memories throughout sleep. An alternative is that sleep forms a temporal micro-structure that facilitates the replay of different memories during specific substates. To test these two hypotheses, we simultaneously recorded large neuronal ensembles in dorsal area CA1 of the hippocampus (up to ~300 neurons), while monitoring sleep dynamics via pupillometry, in naturally sleeping mice (n = 8). Oscillatory pupil fluctuations revealed a previously unknown micro-structure of non-REM sleep, associated with memory processes on an ultraslow timescale (~0.015 Hz). Rather than random interspersion, we found a notable segregation of different replay types coupled to the sleep micro-structure: replay of recent experiences dominated in SWRs during contracted pupil substates of non-REM sleep, while replay of prior memories preferentially occurred during dilated pupil substates. This new finding explains previous observations that replay of recent experiences is restricted to a small fraction of all sleep SWRs.

Furthermore, the contracted pupil substate was associated with stronger extrinsic excitatory inputs from CA3 and entorhinal cortex, whereas higher recruitment of local inhibition within CA1 was prominent during dilated pupil substates. Therefore, the micro-structure of non-REM sleep that we uncovered may provide a fundamental neural mechanism for the consolidation and integration of multiple memories without interference.

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Poster

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Title: Closed-loop manipulation of sharp-wave ripples reveals cortical readout dynamics of hippocampal memory reactivation.

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Abstract: Classical models of memory formation posit that new memories are initially encoded in the hippocampus during waking and subsequently consolidated during sleep for long-term storage in the neocortex. However, recent evidence suggests that memory encoding and consolidation involve bidirectional interactions between these structures rather than a purely unidirectional process. A limitation of previous studies addressing this issue was the lack of simultaneous neural ensemble recordings across structures together with specific manipulations of cross-regional interactions.
SWRs are synchronous hippocampal network events that reactivate experience-related neuronal activity patterns and support learning and memory processes. Previous work showed that the subset of SWRs with a longer duration during waking is specifically important for memory formation. Yet, how these longer SWRs contribute to memory consolidation and mediate memory reactivation in the neocortex remains unexplored.
To casually test how hippocampo-cortical ensemble coordination during SWRs contributes to memory formation and recall, we performed dual hippocampal-prefrontal cortex (mPFC) silicon probe recordings in mice together with closed-loop optogenetic manipulations of SWR-related activity in both structures. We found that SWR duration increased following learning. Moreover,

we found that enhanced reactivation of task-related mPFC cell assemblies occurred consistently following SWRs with specific features, suggesting a differential cortical readout of specific subtypes of hippocampal SWRs. To test whether SWR-related cortical reactivation immediately after learning is needed for subsequent memory consolidation, we silenced the mPFC during SWRs using a closed-loop optogenetic approach. This manipulation, but not when delivered at random times, impaired recall. We next extended the length of SWRs optogenetically, resulting in an improved memory recall. This improvement was blocked by simultaneously inhibiting the PFC during hippocampal SWR boosting.
Together, these data suggest that initial cortical reactivation during SWRs is necessary for subsequent memory consolidation and recall. These data further suggest that mPFC assemblies are preferentially reactivated by specific SWR subtypes, suggesting specialized functional roles for different SWR

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Poster

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Title: A Hippocampal-parietal Network for Rapid Map to Action Transformation

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Abstract: Movement through space and establishing memories based on these experiences are essential for survival of animals including humans. This ability is thought to require storage of memories often in an allocentric (map-like) framework and conversion to a body-centered reference frame comprised of specific actions. These frameworks are coordinated in a fluid manner during navigation. The encoding observed in hippocampus (HPC) and parietal cortex (PC) has led to the notion that this circuit is part of a coordinate transformation network (e.g., transforming a remembered allocentric representation into the appropriate action). While HPC neurons are typically modulated by allocentric locations, PC neurons are modulated by multiple

reference frames including actions (e.g., right turn). We tested this hypothesis with a*complex spatial sequence task* where rats learn to navigate to unmarked locations fixed in space in a sequence. Landmarks are distributed in the room for spatial orientation. We use a sequence (**1-2-3**-4-**1-2-3**-5-) that has a repeating path segment (**1-2-3**) followed by one of two distinct actions. The rat learns in context 5-**1-2-3**-4, to go to 4 for reward, while in context 4-**1-2-3** the rat must go to 5. This emulates the spatial memory problem one encounters when driving through an intersection and remembering the appropriate action given the current route and goals (e.g., turn left to bank versus right to home). Rats are trained to perform unguided ('memory') runs through the complete **1-2-3**-4-**1-2-3**-5 sequence. Following an error, a light cue directs the rat to the next zone in the sequence. Thus, the rat must coordinate between remembered allocentric context and egocentric action. We found that for the 1-2 segment, HPC units encode spatial memory information (i.e. allocentric context; came from zone 4 vs 5). Surprisingly, this signal is also apparent in PC during the 1-2 segment suggesting allocentric context is conveyed to PC. Subsequently, information about the upcoming action is apparent in PC, most prominently during the 2-3 segment. Finally, this transformation from an allocentric context to upcoming choice representation happens gradually with the allocentric context signal fading and the upcoming choice signal strengthening over the 1-2-3 segment. A final surprise was that a signal for the upcoming action is apparent in HPC after the signal is in PC. This HPC signal differs in that it is a direct allocentric trajectory to the goal and not the actual route taken. Thus, we provide evidence that the HPC-PC network may enable coordinate transformation and that signals for map like and person-centered reference frames travel bidirectionally between the PC and HPC.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

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Title: Longitudinal characterization of resting state fMRI, DTI, and action-place spatial learning in the TgF344-AD rat reveals impaired action-place learning emerging at 5-months

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Seattle, WA; [4]Florida State Univ., Tallahassee, FL; [5]Psychology, Florida State Univ. Program In Neurosci., Tallahassee, FL

Abstract: A hallmark of preclinical Alzheimer's Disease (AD) is spatial disorientation, such as getting lost in new locations. One potential cause is disrupted exchange between egocentric and allocentric reference frames. Both the parietal (PC) and retrosplenial cortex (RSC) are known for roles in encoding/transforming information between these reference frames. The RSC and PC are also earlier sites of dysfunction in humans with AD and rodents modeling aspects of AD. This study aimed to examine resting-state functional MRI (rsfMRI) and the relationship with coordination between reference frames in a rat model of AD. We hypothesized that pathology development in TgF344-AD rats lead to brain network dysfunction, which causes impaired allocentric/egocentric coordination.

In TgF344-AD rats and littermate controls, reference frame coordination was assessed at 3, 5, & 8.5 months with an action-oriented spatial navigation task. Rats were required to associate actions (e.g., left turn) with locations. Days to criterion, number correct, incorrect and no response, side bias, head scanning, and procedural errors were measured. Graph theory was applied to longitudinal MRI data acquired at 2, 4, 6, 10, 12, 16 & 18 months *in vivo* at 21.1T to assess functional and structural connectivity alterations by rsfMRI, and structural diffusion tensor imaging (DTI), respectively.

We found that at 3-months, rats in both groups could not achieve criterion and declines in action-orientation performance emerged at 5-months of age. These alterations coincided with changes in the hippocampus and the entorhinal cortex of TgF344-AD rats, with a delay in changes in weighted degree to later in life than controls. At 5 months, the TgF344-AD animals made fewer correct choices and had more no response trials than littermate controls. Further, head scanning was reduced in Tg animals. However, none of these behavioral impairments were sustained at 8-months for any measure. To explore this lack of impairments at 8-months, we assessed performance within group across age. When comparing age x day interactions, both groups made more correct choices at 8-months and 5-months compared to 3-months. Overall, we saw group differences in number of correct responses as animals age. Additionally, amyloid aggregation appears to increase as animals age between 5 and 8 months. Together, this pattern of results suggests that repeated testing may ameliorate impairments in 8-mo TgF344-AD rats. A cross sectional study is underway to test this hypothesis. These findings highlight a new focus for understanding cognitive deficits in AD by using allocentric and egocentric coordination as a novel predictor of early declines in AD.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

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Support: FL DOH 20A09
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Title: Resting after learning facilitated memory consolidation and reversed impairments in getting oriented in 'new surroundings' in 3xTg-AD mice

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Abstract: An essential component of productive memory consolidation and waste product clearance, including pathology associated with Alzheimer's disease (AD), is sleep. Poor sleep is associated with increased amyloid beta (Aβ) and tau proteins, poor cognition, and an increased risk of AD; whereas facilitation of sleep decreases Aβ and tau accumulation. Sleep also plays a significant role in the consolidation of memories, including spatial memories. Brain dynamics during rest are disrupted in 3xTg-AD female mice and contribute to impaired spatial navigation behavior (Benthem et al 2020). Thus, improving rest may offer a multifaceted approach to improving cognition and slow or halt disease progression in those at risk for AD. However, studies assessing sleep impacts on AD often fail to assess cognition.Getting lost, particularly in new surroundings, is an early impairment in humans that develop AD. Recent work, including our own, suggests that this early impairment could represent a failure to use distal cues to reorient in space (Stimmell et al., 2019), impaired consolidation of memories during sleep (Benthem et al., 2020), or likely both. Thus, we set out to assess the impact of rest on impaired spatial reorientation previously observed in 6-month female 3xTg-AD mice. We randomly assigned 3xTg-AD mice to a rest (n = 7; 50 min pre- & post-task induced rest) or a non-rest group (n= 7; mice remained in the home cage pre- & post- task). Mice in both groups were compared to non-Tg age matched non-rest controls (n=7). Finally, to confirm that our sleep condition induced sleep, we performed the same experiment in 3xTg-AD and control mice (n=6/group) implanted with a recording array with electrodes in the hippocampus to record local field potentials which were used to classify sleep states. Markers of pathology were also assessed in the parietal-hippocampal network. We previously showed that pTau positive cell density predicts spatial reorientation ability (pTau, 6e10, M78, M22, as in Stimell et al., 2020, but here automatically counted with Zeiss ZEN 3.7 software). We found that 6-month female 3xTg-AD sleep mice (both with and without a recording array) were not impaired at spatial reorientation, while 6-month female 3xTg-AD no sleep mice were impaired at spatial reorientation learning, a replication of Stimmell et al., 2019. This recovered behavior persisted, despite no change in the density of pathology positive cells. Taken together, our data suggests that sleep may be capable of reversing cognitive impairments that occur as a consequence of tau and Aβ aggregation, but by enhancing memory consolidation, and not altering tau or Aβ levels directly.

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Poster

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Title: Altered sleep and low delta during sleep in young 3xTg mice and TgF344 rats may offer insight into early risk markers for progression to Alzheimer's Disease

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Abstract: The brain, unlike the other systems of the body, does not have a conventional lymphatic filtration system (Xie et al., 2013). Rather it is thought that extracellular waste is cleared by the coordinated effects of cerebrospinal fluid (CSF) and the astrocytes of the blood brain barrier (Xie et al., 2013). Circulating CSF flows into the brain along the perivascular space surrounding cerebral arteries (Iliff et al., 2013). Fluid then travels through the brain parenchyma through water channels on astrocytic end-feet, collecting free-floating material in the extracellular matrix (Iliff et al., 2013). Travelling back through astrocytic channels, waste leaves the brain as interstitial fluid (ISF) along the perivascular space surrounding venules (Iliff et al., 2013). While this 'glymphatic' system is thought to be active at all times, the oscillations generated by slow wave sleep (SWS) are thought to provide the optimal environment for clearance by enhancing the flow rate of circulating fluid (Mander et al., 2016). Alzheimer's Disease is the most common form of dementia and is characterized by aggressive intra- and extracellular protein aggregations that yield devasting effects (Mander et al., 2016). Most well-known for its impacts on cognition, early markers for Alzheimer's have long been associated with sleep deficits and impairments in spatial navigation (Mander et al., 2016). Improving the brain's glymphatic system may therefore provide an innate protection against natural or induced forms of cognitive decline. Recently, our lab has found sleep deficits in 6-month-old female 3xTgAD mice. Despite reports of sleep fragmentation at later ages, we found episodes of SWS were extended at this early stage. However, the ratio between theta (7-10 Hz) and delta (0-4 Hz) power was heightened at the transitions into and out of SWS, and throughout entire sleep periods, suggestive of a dampened circadian clock and lower sleep depth. These deficits were found to be a significant predictor of spatial learning and memory, as higher power (i.e., poorer

sleep) was associated with worse spatial learning and memory in 3xTgAD mice. We have replicated these sleep changes and found a similar behavioral impairment in the TgF344AD rat models. Work is underway to treat these deficits by targeting the orexinergic pathway, an established regulator of the sleep/wake cycle. Previously shown to enhance SWS, we hypothesize that the administration of a dual orexin receptor antagonist (DORA) agent can help restore healthy sleep characteristics in 3xTgAD mice by increasing glymphatic flow. We are also assessing the impact of DORAs on glymphatic flow in 3xTgAD and NonTg mice.

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Poster

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Title: Spatial and contextual coding along the CA3 dendritic tree

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Abstract: Anatomically segregated apical and basal dendrites of pyramidal neurons receive functionally distinct inputs, but it is unknown if this results in compartment-level functional

diversity during behavior. Hippocampal place cells exhibit remapping when exposed to new environments or changes in task parameters. Remapping occurs on very fast timescales, well beyond the temporal regime of typical plasticity mechanisms. Multiple studies implicate active dendritic spikes in predicting the formation of stable place fields and shaping hippocampal activity. However, in vivo studies of hippocampal dendritic activity have largely been confined to basal dendrites and small cross sections of apical dendrites. Here we imaged calcium signals from apical dendrites, soma, and basal dendrites of pyramidal neurons in area CA3 of mouse hippocampus during head-fixed navigation. This visually stunning preparation allows simultaneous imaging of the entire dendritic tree of CA3 pyramidal neurons, offering an unparalleled opportunity to study spatial and contextual coding properties along the dendritic axis. To probe dendritic spatial selectivity amid contextual changes we introduce the Möbius belt, a treadmill belt with different tactile cues on either side of the belt allowing context switching during continuous recording of head-fixed mice. Sparse expression of GCaMP allowed us to image calcium activity of soma and dendrites of individual excitatory neurons in hippocampal area CA3, as well as dendrite-targeting somatostatin-expressing inhibitory neurons. Both soma and dendrites altered their activity in response to contextual changes, with some cells showing total cessation of activity in one of the contexts. In any given context there was a reliable decrease in activity rate as a function of distance from the soma in both apical and basal dendrites. Calcium transient dynamics were also much more rapid in dendrites, on the order of 50-100 ms in distal compartments, compared to seconds-long somatic transients, underscoring the need to perform imaging at adequate sampling rates to capture the intricacies of dendritic activity. To examine dendritic population activity we expressed GCaMP more densely, recording thousands of dendritic branches simultaneously. To analyze this data we developed computational tools – collectively named “Dendritic Non-negative Matric Factorization” (DNMF) – to automatically identify dendritic regions of interest and extract accurate fluorescence traces from densely labeled preparations. These tools will facilitate future studies of signal transformations between cellular compartments and their relation to behavior.

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Poster

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Title: Integration of Entorhinal Cortices in Hippocampal Area CA3

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Abstract: Our memories rely on the association of information from different sensory modalities but how this information is combined to contribute to memory formation and recall remains an open question. The entorhinal cortex provides complex sensory information to the hippocampus and is subdivided into the lateral (LEC) and medial entorhinal cortex (MEC). Longstanding dogma assumes that the association of place (MEC) and context (LEC) is key to forming accurate and long-lasting hippocampal representations. Most studies emphasize their segregated functional roles, leaving the mechanism of their integration largely understudied. These two inputs appear to converge in a specific subfield of the hippocampus, area CA3. To understand how space and context are implemented in the episodic memory system I look at the functional, circuit interactions of LEC and MEC inputs to CA3. For this, I used dual-color optogenetic stimulation of LEC and MEC inputs and *ex vivo* whole-cell patch-clamp recordings from CA3 pyramidal neurons together with pharmacology to examine the input-output transformation operated by this circuit. I found that every CA3 pyramidal neuron recorded was monosynaptically connected to both MEC and LEC inputs. Recordings of excitatory and inhibitory postsynaptic currents suggest MEC recruits more excitation and inhibition than LEC, fitting with its anatomically more proximal location. Though stimulation of an individual input (MEC or LEC) does not lead to action potential generation, in a subpopulation of CA3 pyramidal neurons, simultaneous or near-simultaneous (0.1-10ms) stimulation of both inputs can lead to somatic output. This suggests synchronization of EC inputs with CA3 firing may require MEC and LEC coincident activity, a phenomenon thought to be responsible for efficient transfer of information from one brain region to another. Ongoing experiments to find the mechanism for 'filtering' and/or integrating the signal from LEC and MEC indicate that these inputs recruit overlapping interneuron subtypes. We postulate that LEC and MEC recruit these overlapping circuits in a frequency dependent manner allowing each input to convey region specific information to an individual neuron. My study provides both structural and functional information about the circuitry that is involved in combining complex sensory information in service of episodic memory formation and recall.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

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Title: Long-range Glutamatergic and GABAergic inputs control discrimination and generalization in CA3

Authors: *V. ROBERT[1], K. M. O'NEIL[2], S. K. RASHID[1], C. JOHNSON[3], R. G. DE LA TORRE[4], B. ZEMELMAN[5], C. CLOPATH[6], J. BASU[7];
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Abstract: Functional interactions between the entorhinal cortex and the hippocampus are crucial for learning and memory. By integrating context-laden direct inputs from the lateral entorhinal cortex (LEC) with local feedforward dentate gyrus (DG) and feedback CA3 inputs, area CA3 is poised to gate hippocampal information flow and mnemonic function. Interestingly, LEC inputs to the hippocampus comprise not only glutamatergic (LEC_{GLU}) but also long-range GABAergic (LEC_{GABA}) projections which have been shown to regulate dendritic excitability, synaptic plasticity and oscillatory activity in area CA1. However, the role of LEC_{GLU} and LEC_{GABA} inputs in shaping area CA3 activity and function and their underlying circuit elements remains unexplored. We first chemogenetically manipulated LEC inputs to CA3 while mice performed freely moving and head-fixed behavioral learning tasks which revealed complementary rather than opposing roles of the LEC_{GLU} and LEC_{GABA} inputs in novelty and spatial context discrimination. Two-photon calcium imaging of CA3 pyramidal cell soma and dendrites *in vivo* during a context-dependent goal-oriented spatial navigation task, however, revealed a bidirectional modulation of their activity by LEC_{GLU} and LEC_{GABA} inputs. Counterintuitively, silencing LEC_{GLU} inputs alone increased CA3 activity, suggesting predominant recruitment of local feed-forward inhibition. We examined the underlying circuit mechanism using *ex vivo* functional mapping with dual-color optogenetics to selectively activate LEC_{GLU} and LEC_{GABA} inputs. Recordings from CA3 pyramidal cells showed that LECGLU inputs evoked

monosynaptic direct excitation and disynaptic feed-forward inhibition, which prevented CA3 somatic output. Indeed, LEC_{GLU} inputs drove spiking in CA3 SLM interneurons, including putative soma-targeting subtypes, whereas LEC_{GABA} inputs shunted their excitability. Activating LEC_{GABA} projections selectively boosted CA3 pyramidal neuron somatic output to combined stimulation of LEC_{GLU} and CA3 recurrent collaterals but not DG inputs. *In vivo* manifestation of such pathway-specific disinhibition included impaired remapping of CA3 place cell ensembles with silencing of LEC inputs. Together with *in silico* modeling of attractor dynamics, this suggests that LEC_{GLU} vs LEC_{GABA} promote discrimination vs generalization of CA3 representations, respectively. Taken together, our results uncover long-range cortico-hippocampal circuit interactions gating compartment- and pathway-specific excitation, inhibition, and disinhibition to support spatial and contextually driven CA3 activity *in vivo* and memory functions.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.17/N2

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Title: Role of LEC Glutamatergic and GABAergic projections into Hippocampal area CA1 in episodic memory

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Abstract: Interaction between the entorhinal cortex and hippocampal area CA1 promotes sequential organization of information flow and non-linear computations such as dendritic spikes

and plasticity to support the formation of episodic memories of people, places, objects, and events. Within the entorhinal cortex, the medial part (MEC) processes spatial information and conveys this input about position in space, head direction, borders, and speed to the hippocampus. Whereas the lateral entorhinal cortex subdivision (LEC), codes for contextual non-spatial sensory cues in the environment, and routes information related to objects and their location, novelty, salient contexts such as rewards and punishments, temporal and rule structures of learning tasks, and odors to the hippocampus. Both LEC and MEC send Glutamatergic excitatory and GABAergic inhibitory projections directly to HC-CA1. We have recently mapped the microcircuit connectivity of these projection inputs and revealed activity-dependent cellular mechanisms by which LEC modulates the dynamics of excitation- inhibition -disinhibition within CA1. However, we know little about the functional role of these projections in episodic memory modulation and supporting behavioral output. To address this function, I used chemogenetic strategies to silence the Glutamatergic and GABAergic projections from LEC locally in CA1 during a contextual learning behavior, Novel Object Recognition (NOR), a spatio-contextual learning behavior- Novel Object Location (NOL) task and one spatial memory behavior, the Barnes Maze (BM). Next, with fiber photometry recordings in the same freely moving behaviors, I determined the functional activity of these direct Glutamatergic and GABAergic projections during the encoding and recall phases of these behaviors. Our results suggest that the population level activity of Glutamatergic and GABAergic projections between LEC and HC-CA1 are modulated at differential epochs during encoding and recall phases of the contextual and spatial task aspects and serve differential memory functions.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

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Topic: H.08. Learning and Memory

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2022 Foerderer Fund for Excellence Award (PI: Van Batavia)
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2023 Penn College Alumni Society Board of Managers and President's Undergraduate Research Grant (PI: HA Haas)

Penn Vagelos Program (AIM)
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Title: Dissecting the role of lateral entorhinal cortex-dentate gyrus circuit in the memory encoding and consolidation of behavioral pattern separation in mice

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Abstract: Each memory stage plays a crucial part in successful memory formation, and similar episodes are more difficult to remember than dissimilar episodes. Behavioral pattern separation (BPS), the ability to discriminate highly similar episodes, allows for greater memory resolution. Patients with several psychiatric or neurological disorders exhibit impaired BPS. Studying BPS-related neural circuitry will aid in understanding complexed episodic memory processes and developing treatments for these disorders. Our published work suggests that chronic stimulation of the lateral entorhinal cortex (LEC)-dentate gyrus (DG) glutamatergic circuit improves BPS in male mice, using a repetitive BPS test. However, it is unknown how this circuit impacts BPS in memory stage-specific manners. In rats, the DG is involved in the memory encoding and the initial consolidation stages of one-trial BPS tests. We hypothesized that the inhibition of the terminals of LEC fan cells that provide direct inputs to the DG during the memory encoding and/or initial consolidation will decrease BPS in mice. To test this hypothesis, we utilize the spontaneous location discrimination test (SLR), a one-trial BPS test that relies on the mouse's innate ability exploring novel location of the object based on external spatial cues. SLR consists of a 10 min Sample phase followed by a 35 min Delay and a 5 min Test phase. SLR was executed at three levels of memory load by varying object separation degrees in Sample-low (d-), medium (s-) and high (xs-) memory loads. First, to optogenetically inhibit the terminals of the LEC fan cells in the encoding phase, 9-week-old Sim-1cre+; ArchT2flox/- [Cre+] and Sim-1cre-; ArchT2flox/- [Cre-] male and female mice received bilateral optic fibers in the DG molecular layer. Two weeks post-surgery, light (530 nm) was delivered during the Sample phase. We found a lower discrimination index (d2 ratio) in Cre+ males relative to Cre- males in s-SLR but not female mice. A similar index was seen in both groups in d-SLR. This suggests the LEC inputs to the DG is required for BPS ability in male mice. Second, to test the circuit's requirement in the initial consolidation phase, a second cohort of male and female mice received the same treatment but the light was delivered during the first 10 minutes of Delay phase. We found both groups have a similar d2 ratio in any memory loads, implying that the LEC inputs to the DG during the initial memory consolidation phase is not required for BPS. By understanding the distinct role of the LEC in BPS memory stages, our study will provide a novel therapeutic efficacy for BPS deficits in many disorders.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.19/N4

Topic: H.08. Learning and Memory

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2021 NASA HERO grant and Augmentation Award (80NSSC21K0814, PI: S Yun)
2022 Foerderer Fund for Excellence Award (PI: J Van Batavia)
CHOP junior faculty pilot grant (PI: J Van Batavia)
2023 Penn College Alumni Society Board of Managers and President's Undergraduate Research Grant (PI: HA Haas)
Special thanks to an anonymous donor who has provided support for the Eisch Lab and this project.

Title: In vivo recording of mouse lateral entorhinal cortex fan cells after stress: insight into subanesthetic ketamine's antidepressant ability

Authors: *H. A. HAAS[1,2], G. BANCROFT[3], N. BABIKER[4], S. YUN[5], A. J. EISCH[6];
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Abstract: Dysregulated hippocampal circuitry is proposed to contribute to the stress-induced dysregulation of mood and cognition seen in depressive disorder. Our two-part pilot data suggest the importance of lateral entorhinal cortex (LEC) neurons in response to stress: 1) stimulation of mouse LEC fan cells (which project to the dentate gyrus, DG) ameliorates stress-induced depressive-like behaviors and hippocampal-dependent learning; and 2) one prior injection of subanesthetic ketamine (sa-KET) improves stress-induced reduction of DG-dependent learning. Here using awake, behaving mice and in vivo miniature microscopy imaging, we asked two questions raised by these pilot data: How does prior acute stress influence LEC fan cell activity? And how does sa-KET influence stress-induced changes in LEC fan cell activity? Seven-wk-old Sim1-cre mice received a unilateral LEC infusion of a virus expressing a cre-dependent GCaMP6f and GRIN lens implantation. On Day 1, LEC Ca2+ transients evoked in a novel arena were measured twice for 10-min: at Baseline and Post-stress (after 30-min restraint stress followed by saline injection). On Day 2, the procedure was repeated with sa-KET (15 mg/kg, i.p.) instead of saline. For this within-mouse study, Ca2+ transient signals at the single-cell level were analyzed using validated Minian and CellReg pipelines. Stress effect. On Day 1, LEC fan cells were less active Post-stress vs. Baseline (decreased z-scores in spike rate and amplitude; n=47-62 cells). For paired cells (those detected at both Baseline and Post-stress), 72% (21/29) were less active (decreased z-scores in spike rate and amplitude) Post-stress vs. Baseline. Saline vs. sa-Ket Post-stress. Comparing the Post-stress signals on Day 1 (Saline) vs. on Day 2 (sa-Ket),

60.7% (17/28) paired cells were more active (56% higher spike rate z-score) in sa-KET vs. Saline, but 39.3% (11/28) paired cells were less active (118% lower spike rate z-score) in sa-KET vs. Saline. These results show both acute stress and sa-KET have a rapid effect on the activity of single LEC fan cells, which are ideally positioned to change DG activity and provide a potential neuronal mechanism for how sa-KET influences stress-induced hippocampal-dependent cognition.

Disclosures: H.A. Haas: None. **G. Bancroft:** None. **N. Babiker:** None. **S. Yun:** None. **A.J. Eisch:** None.

Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

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Topic: H.08. Learning and Memory

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Special thanks to an anonymous donor who has provided support for the Eisch Lab and this project.

Title: How does lateral entorhinal cortex fan cell activity change between encoding and retrieval for different pattern separation memory loads?

Authors: *N. BABIKER[1], E. DELLINGER[2], G. BANCROFT[3], H. HAAS[4], S. YUN[5], A. J. EISCH[6];
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Abstract: Behavioral pattern separation (BPS) is the ability to discriminate between similar stimuli. BPS is sensitive to “load”; greater similarity, harder to distinguish, higher BPS load. BPS is poor in humans with normal aging and in various neuropsychiatric disorders, and in

humans and rodents when the neural pathway between the entorhinal cortex (EC) and the hippocampal dentate gyrus (DG) is disrupted. In contrast, BPS is improved when the lateral EC (LEC) fan cells projecting to the DG receive chronic stimulation. Our pilot data show LEC-DG activity necessity during BPS is memory-stage specific: DG terminal activity of LEC fan cells is required during encoding but not consolidation. To advance our exploration of the role of LEC-DG activity in the stages of BPS, here we measured LEC fan cell Ca2+ transients in awake, freely-moving mice during the encoding and retrieval phases of a single-trial BPS test, spontaneous location recognition (SLR). 8.5 wk-old Sim1-Cre mice (n=1 male) received LEC infusion of AAV9-CAG-flex-GCaMP6f and GRIN lens implantation. 9-wks post-surgery, mice underwent SLR (10-min Sample/Encoding, 35-min Delay/Consolidation, 5-min Test/Retrieval) with identical objects that were placed during Sample far apart (different, d-SLR) and then close together (similar, s-SLR). Ca2+ transient signals at the single-cell level were analyzed using validated Minian and CellReg pipelines, and data from one mouse is presented here. During s-SLR (high memory load), 30% of cells (42/139) were detected in Sample, but not Test; 28.7% of cells (40/139) were detected in Test, but not Sample; and 41.0% of cells (57/139) detected were "paired" (present in both Sample and Test). LEC fan cells showed increase spiking for sSLR in Sample vs Test phase (49.6% higher Z-score in spike rates; n=99-134 cells, t-test, *P=0.018), with no change in amplitude. However, during d-SLR (low memory load), LEC fan cells had similar activity in both phases (Z-score in spike rates, n=102-134 cells, t-test, P=0.9). Analysis of LEC fan cell activity during exploration of objects in novel vs. familiar locations in both phases and processing of data from additional mice is underway. These data lay the groundwork for understanding the role of the LEC-DG in BPS.

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Poster

PSTR138: Learning and Memory: Hippocampal-Cortical Interactions I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR138.21/N6

Topic: H.08. Learning and Memory

Support: NIH R01 MH123466

Title: Paradoxical replay can protect contextual task representations from destructive interference when experience is unbalanced

Authors: *H.-T. CHEN, M. A. VAN DER MEER;
Dartmouth Col., Hanover, NH

Abstract: Experience replay is a powerful mechanism for efficient learning from limited experience. However, despite decades of compelling experimental results, the factors that determine which experiences are selected for replay remain unclear. A particular challenge arises

in tasks with highly unbalanced experience, where rats replay trajectories that neither reflect recently chosen choices nor predict upcoming ones. This paradox challenges the conventional view of replay's role in memory consolidation (a retrospective process) and planning (a prospective process), which suggests that hippocampal replay content should closely align with recent experience.
Drawing from insights in a largely separate computational literature, which demonstrates that unbalanced training makes memory storage in neural networks susceptible to destructive interference, we propose a specific hypothesis for the function of *paradoxical replay*: to protect memories from the detrimental effects of unbalanced experience. To test this hypothesis, we first simulated a feedforward neural network with two learning regimes: *rich learning*, characterized by slow learning speed but resulting task-specific representations that are more robust to noise, and *lazy learning*, marked by fast learning but resulting task-agnostic representations that are less robust to noise. We found that rich, but not lazy, representations degraded following unbalanced experience, an effect that could be reversed with paradoxical replay.
To validate this computational principle with experimental data, we investigated the relationship between paradoxical replay and learned task representations in the hippocampus. Remarkably, we observed a strong association between the richness of learned task representations and the occurrence of paradoxical replay. These findings suggest that paradoxical replay specifically serves to protect rich representations from the destructive effects of unbalanced experience, highlighting a novel interaction between the nature of task representations and the function of replay in both artificial and biological systems.

Disclosures: H. Chen: None. **M.A. van der Meer:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.01/N7

Topic: H.08. Learning and Memory

Title: Investigating the Epigenetic Mechanisms underlying Memory Consolidation during Sleep

Authors: *X. CHEN[1], A. MALDONADO RODRIGUEZ[2], W. ZHOU[4], B. UCEDA-ALVAREZ[2], F. RUAN[5], Y. PENG[2], S. LIU[3];
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Abstract: Sleep after learning something (“post-learning sleep”) actively consolidates what was learned, and sleep deprivation after learning impairs memory performance. Yet, the underlying cellular and molecular mechanisms of these processes remain elusive. We aim to address this question using the fear conditioning (FC) behavior as a memory paradigm. From the cellular aspect, we use cFos-based approach to label and examine the potential memory engram cells

during FC memory encoding and recall in brain regions such as the Basolateral Amygdala (BLA), Hippocampus, and Anterior Cingulate Cortex (ACC). At the molecular level, we proposed to test one of the epigenetic mechanisms, DNA methylation, as a potential memory substrate. We hypothesize that DNA methylation alters expression of memory-regulating genes in engram cells during post-learning sleep to facilitate memory consolidation. Here, we present our preliminary data showing that: (1) the necessity of Dnmt3a in memory encoding cells for fear memory recall; (2) sleep deprivation alters cellular reactivation in FC-related regions during fear memory recall; (3) using Whole Genome Bisulfite Sequencing (WGBS), we identified differentially methylated regions (DMRs) during memory formation. In conclusion, our data suggests that BLA engram neurons may regulate fear memory consolidation during post-learning sleep via DNA methylation. These results shed light on the role of epigenetic mechanisms in sleep-dependent memory consolidation.

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Poster

PSTR139: Molecular Mechanisms of Memory

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.02/N8

Topic: H.08. Learning and Memory

Support: Research Council of Norway (NO.326101)

Title: The role of TDG-mediated DNA demethylation in hippocampus-dependent memory

Authors: *D. DØSKELAND[1], V. SAASEN[1], M. BJØRÅS[1,2], J. YE[1];
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Abstract: The dynamic regulation of DNA methylation (mC) and hydroxymethylation (hmC) is associated with various hippocampus-dependent memory processes. hmC, an oxidized form of mC, is an essential intermediate in the active DNA demethylation pathway. The further oxidized hmC derivatives are eventually removed by the thymine DNA glycosylase (TDG) initiated DNA base excision repair (BER). Constitutive knockout or catalytic inactivation of TDG leads to embryonic lethality in mice, demonstrating an essential role of TDG in the epigenetic regulation of early development. However, we do not know whether TDG impacts the epigenetic plasticity and functional identity of terminally differentiated cells such as neurons. It remains elusive whether TDG-dependent removal of mC derivatives is required for encoding, associating, consolidating, and retrieving distinct memories. In this study, we utilized the Cre-LoxP system, specifically driven by the CamkIIα promoter, to achieve conditional knockout of Tdg in excitatory neurons in mice after birth. CamKIIα-miniTdg-/- mice exhibited marked TDG depletion in hippocampal neurons, initiated from postnatal day 19 (P19) and persisting into

adulthood. The specificity of TDG deletion was characterized by immunohistochemistry, RT-qPCR, and Mass Spectrometry-based analysis of oxidized hmC derivatives such as fC and caC. Furthermore, we employed single-nuclei RNA sequencing (snRNA-Seq) with the cutting-edge split-pool combinatorial barcoding technology to profile transcriptomic differences in TDG-depleted hippocampal neurons at two postnatal time points: P19 (immediate after TDG depletion) and P30 (approximately 10 days post-depletion). Meanwhile, we established different behavioral tasks, including the Novel object location task, Reward memory task, Radial Arm Maze, and Fear Conditioning test, to evaluate the effects of TDG depletion on hippocampus-dependent memory processes. Our preliminary results suggest that TDG may play a role in memory extinction. We will isolate hippocampal neurons from control and Tdg-/-mice following the behavioral task for a comprehensive transcriptomic and epigenomic analysis. We aim to uncover TDG-dependent epigenetic mechanisms underlying hippocampal function in memory.

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Poster

PSTR139: Molecular Mechanisms of Memory

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Canada Graduate Scholarship – Doctoral from the Natural Sciences and Engineering Research Council
NeuroImaging and NeuroComputation Centre at the Djavad Mowafaghian Centre for Brain Health (RRID: SCR_019086)
Janelia Visiting Scientist Program

Title: The cell-type-specific spatial organization of the anterior thalamic nuclei of the mouse brain

Authors: *J. TSAI[1], M. KAPUSTINA[1], A. A. ZHANG[1], B. N. BRISTOW[1], L. KRAUS[1], K. E. SULLIVAN[1], S. R. ERWIN[1], L. WANG[5], T. R. STACH[2], J. CLEMENTS[5], A. L. LEMIRE[5], M.

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[1]Dept. of Cell. and Physiological Sci., [2]Sch. of Biomed. Engin., [4]Djavad Mowafaghian Ctr. for Brain Hlth., [3]Univ. of British Columbia, Vancouver, BC, Canada; [5]Janelia Res. Campus, HHMI, Ashburn, VA

Abstract: Understanding the cell-type composition and spatial organization of brain regions is crucial for interpreting brain computation and function. In the thalamus, the anterior thalamic nuclei (ATN) are involved in a wide variety of functions, yet the cell-type composition of the ATN remains unmapped at a single-cell and spatial resolution. Combining single-cell RNA sequencing, spatial transcriptomics, and multiplexed fluorescent in situ hybridization, we identify three discrete excitatory cell-type clusters that correspond to the known nuclei of the ATN and uncover marker genes, molecular pathways, and putative functions of these cell types. We further illustrate graded spatial variation along the dorsomedial-ventrolateral axis for all individual nuclei of the ATN and additionally demonstrate that the anteroventral nucleus exhibits spatially covarying protein products and long-range inputs. Collectively, our study reveals discrete and continuous cell-type organizational principles of the ATN, which will help to guide and interpret experiments on ATN computation and function.

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Poster

PSTR139: Molecular Mechanisms of Memory

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Program #/Poster #: PSTR139.04/N10

Topic: H.08. Learning and Memory

Support: Research Council of Norway (No. 326101)

Title: Disrupted Neural Circuitry in NEIL3 Knockout Mice and Its Implications for Hippocampal Function and Memory

Authors: *M. FERNANDEZ BERROCAL[1], V. SAASEN[1], D. S. DØSKELAND[1], A. M. BUGAJ[2], N. KUNATH[2], M. MUNIR[1], M. BJØRÅS[1], J. YE[1];
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Abstract: NEIL3 DNA glycosylase is an important enzyme that initiates DNA base excision repair (BER) ensuring DNA integrity in the brain. Previous research from our group identified an important role of NEIL3 in shaping hippocampal transcriptome, modulating the stability of hippocampal place cells, and influencing hippocampal functions in spatial memory. Differential gene expression was detected in NEIL3-deficient hippocampal subregions, with emphasis on genes associated with synaptic functions. Specifically, metabotropic glutamate receptors (mGluR), such as GRM2, GRM3, and GRM8, were significantly upregulated in hippocampal

CA1 and DG, suggesting increased excitatory neurotransmission. In contrast, GABA-A receptor subunit alpha2 (GABRA2) was downregulated throughout the hippocampal subregions after NEIL3 depletion, suggesting decreased inhibitory neurotransmission. Notably, we identified that parvalbumin-positive (PV+) GABAergic interneurons were significantly reduced in the *Neil3*$^{-/-}$ hippocampus and medial entorhinal cortex (MEC). Further, we explored the electrophysiological properties of local field potential (LFP) signals in the CA1 region. We observed a significant increase in slow gamma power, potentially reflecting the imbalance in excitatory and inhibitory networks. In assessing hippocampal place cells, we detected a phase preference, with *Neil3*$^{-/-}$ place cells predominantly coupled with the peak of the theta waveform, in contrast to wild-type cells, which were more aligned with the trough of the waveform. These results suggest a potential disruption in the balance of excitatory and inhibitory neural circuits in NEIL3-deficient mice. PV+ interneurons play an important role in timing and synchronizing neural activity necessary for the retrieval and extinction of fear memories. The subsequent analysis involved evaluating *Neil3*$^{-/-}$ mice in the trace fear conditioning task. Our study reveals the non-canonical role function of the DNA glycosylase NEIL3 in modulating hippocampal neural network and synaptic plasticity, diverging from its traditional role in DNA repair.

Disclosures: M. Fernandez Berrocal: None. **V. Saasen:** None. **D.S. Døskeland:** None. **A.M. Bugaj:** None. **N. Kunath:** None. **M. Munir:** None. **M. Bjørås:** None. **J. Ye:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.05/N11

Topic: H.08. Learning and Memory

Support: Wesley Parke Research Award
CBBRe Trainee Research Grant
NIH Grant MH106640

Title: Molecular and behavioral effects of the trophic factors carbamoylated erythropoietin and insulin-like growth factor-1 on cognition

Authors: *M. J. ROTHSCHADL, M. SATHYANESAN, S. S. NEWTON;
Univ. of South Dakota, Vermillion, SD

Abstract: Cognitive functioning plays a significant role in determining an individual's quality of life. Both disease- and age-related cognitive impairments are a growing public health problem, but despite the prominence of cognitive decline, there are limited treatment options, with the current medications failing to show significant and long-lasting cognitive improvements. We seek to understand the role of trophic factors in modulating cognitive function. Trophic factors help modulate neuronal survival, structure, and function, including directly enhancing neuroplasticity. The anti-apoptotic, anti-inflammatory, and neurotrophic properties of trophic

factors could prove beneficial in improving cognition as they target multiple properties associated with cognitive decline. We have shown that the trophic factors carbamoylated erythropoietin (CEPO), a non-erythropoietic derivative of EPO, and insulin-like growth factor-1 (IGF-1) synergistically activate immediate early gene (IEG) expression, including Npas4 and Nptx2. In the brain, IEG upregulation signals the start of changes in synaptic plasticity, which impacts cognitive functioning. In the present study, we examine the temporal pattern of IEG regulation in the hippocampal circuit as a function of trophic factor administration. In addition, we test whether these changes in IEG expression correlate with changes in cognitive behavior. We use a combination of stereotaxic surgery and immunohistochemistry to observe whether intracerebroventricular injection of CEPO + IGF-1 cause synergistic changes in IEG protein expression in the hippocampus of mice at three different time points (30 min, 1 hour, 1.5 hours). We examine p-CREB, cFos, Npas4, and Nptx2 expression in the dorsal and ventral hippocampus. Mouse behavioral assays include novel object recognition, novel object location, and the open field test to investigate the synergistic effects of trophic factor administration in cognitive function. We also conducted a mass spectrometry-based phosphoproteomics analysis to obtain insight into the signaling cascades activated by IGF-1.

Disclosures: M.J. Rothschadl: None. **M. Sathyanesan:** None. **S.S. Newton:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.06/N12

Topic: H.08. Learning and Memory

Support: The startup fund to Hye Yoon Park from the University of Minnesota

Title: A transgenic mouse model for in vivo imaging of endogenous Egr1 mRNA

Authors: *H. AHN[1], D. KIM[2], H. JEONG[1], J. SHIM[2], H. PARK[1];
[1]Dept. of Electrical and Computer Engin., Univ. of Minnesota, Twin Cities, Minneapolis, MN;
[2]Dept. of Physics and Astronomy, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Egr1 is a prominent immediate-early gene (IEG) utilized as a marker for memory encoding and retrieval, yet real-time monitoring of Egr1 mRNA expression in live neurons and animals has not been possible. To address this gap, we have developed a novel knock-in mouse model in which all endogenous Egr1 mRNA is tagged with 12 repeats of MS2 and PP7 binding site (MPBS) pairs. Previous knock-in mouse models using either MS2 or PP7 binding sites (e.g., Actb-MBS(Lionnet et al., 2011; Park et al., 2014) and Arc-PBS(Das et al., 2018; Lee et al., 2022) mice) encountered challenges in *in vivo* brain imaging due to constant background fluorescence from free capsid proteins fused to GFP. To overcome this limitation, we have adopted a background-free RNA labeling strategy using a superfolder GFP (sfGFP) split(Park et al., 2020) into three fragments that reassemble and emit fluorescence only when bound to the

MPBS pairs. Currently, we are characterizing the Egr1-MPBS mouse model and investigating the transcriptional dynamics of Egr1 in mouse embryonic fibroblasts. We anticipate that this innovative mouse model will enable continuous monitoring of the rapid and transient response of the Egr1 gene in live neurons, brains, and freely moving animals.

Disclosures: H. Ahn: None. **D. Kim:** None. **H. Jeong:** None. **J. Shim:** None. **H. Park:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

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Program #/Poster #: PSTR139.07/N13

Topic: H.08. Learning and Memory

Support: NIH Grant 5R01HD103641-03

Title: Spatial transcriptomic profiling of developmental and learning-induced changes in infant mouse dorsal hippocampus

Authors: *J. R. GAUNT[1], M. J. ALU[2], K. RICE[2], C. LOOMIS[2], C. M. ALBERINI[1];
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Abstract: Hippocampal-dependent learning and memory processes undergo substantial changes during development and have been proposed to undergo a critical period. Memories from early life are not explicitly recalled but are stored and affect the encoding of future experiences. Different molecular mechanisms are implicated in learning in infant compared to adult brains, with differences in the regulation of gene and protein expression levels both following events and at baseline. Despite the importance of research into mechanisms of infant learning for understanding cognitive function, the area remains underexplored, with a particular absence of genome-wide profiling studies. We are thus utilizing Visium spatial transcriptomics to profile gene expression with high spatial resolution in the dorsal hippocampus (dHC) and surrounding regions following contextual fear conditioning in infant male C57BL6 mice (1 hour and 24 hours later) and across development in untrained mice (N = 4 biological replicates). The developmental time points represent key stages in the maturation of hippocampal-dependent learning mechanisms: at PN17-18 (corresponding to 2-3 years old in humans), rapid forgetting is observed; at PN24 (corresponding to late childhood/adolescence), the putative critical period closes and long-term memory recall is observed, but the system is not yet mature, and PN90-120 represents the mature adult system. Previous research in our lab studying candidate genes in bulk dHC tissue samples at these timepoints has identified proteins with peak expression at PN24 as well as proteins that show a consistent increase or decrease with age. Bioinformatic analyses of our Visium data identifies novel developmentally-regulated genes and sheds light on the timing and mechanisms of the maturation of hippocampal subregions. Novel genes regulated following an episodic learning event in infants compared to published work in adult mouse dHC are also

revealed for validation and further study. The data provide a wealth of information for research into the mechanisms of infant learning, infantile amnesia, and postnatal brain development, with particular relevance for neurodevelopmental disorders.

Disclosures: J.R. Gaunt: None. **M.J. Alu:** None. **K. Rice:** None. **C. Loomis:** None. **C.M. Alberini:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

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Program #/Poster #: PSTR139.08/N14

Topic: H.08. Learning and Memory

Support: FRM Fondation Line Pomaret Delalande
CNRS
Inserm
Sorbonne Université
Fondation Lejeune

Title: Morphological and behavioural consequences of Shank3 deletion in cerebellar granule cells

Authors: *J. ARCHIMBAUD[1], A. SEBOLD[2], J. ALLÉGRET-VAUTROT[2], N. HECK[3], T. BOURGERON[4], D. A. DIGREGORIO[5], C. ROCHEFORT[6];
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Abstract: Shank3, a protein involved in spine morphogenesis and synaptic transmission, is mainly expressed in the striatum, the prefrontal cortex, the hippocampus and in the granule cells (GC) of the cerebellum. In humans, Shank3 haploinsufficiency leads to the Phelan Mc-Dermid Syndrome (PMS), a rare neurodevelopmental disease with symptoms ranging from motor deficits and intellectual disability to Autism Spectrum Disorder (ASD) in most patients. Many Shank3-global KO mice models have been developed and described, manifesting motor deficits, cognitive and ASD-related disorders. Implication of the cerebellum to these various phenotypes is still unknown, despite growing evidence of a cerebellar implication in cognition and ASD development. To decipher the cerebellum contribution to PMS-associated deficits, we performed a behavioural characterization of adult male and female mice carrying either a global Shank3 deletion (Shank3$^{\Delta 11}$ line) or a Shank3 deletion restricted to cerebellar GC, the Gabra6-Shank3$^{\Delta 11}$ line. We focused our analysis on basic sensory-motor functions and ASD-related behaviours such as social preference and increased stereotyped behaviour through excessive grooming. We found that the lack of Shank3 in the cerebellar GC only does not induce sensory-motor deficits

nor altered social behaviour contrary to what we observed in Shank3$^{\Delta 11}$ global KO mice. However, deleting Shank3 in cerebellar GC induces sex-specific effects with an alteration of grooming behaviour in females. We completed this data with a morphological analysis of Gabra6-Shank3$^{\Delta 11}$ mice. As altered Purkinje Cells (PC) spine density has been previously reported in ASD mice models, we looked at this parameter using a biolistic labelling approach that allowed to sparsely stain distal dendrites of PC, where GC forms synapses. We observed a decreased PC spine density in females specifically, that correlates with our behavioural observations. To evaluate cognition in our lines, we developed a new cerebellum-dependant navigation task in the Starmaze, where we observed altered learning and flexibility in Shank3$^{\Delta 11}$ mice. We aim at probing Gabra6-Shank3$^{\Delta 11}$ mice in this task to study the consequences of Shank3 deletion in cerebellar GC on cognitive abilities and behavioural flexibility. Taken together, our results suggests that deleting Shank3 in cerebellar GC only has sex-specific morphological and behavioural effects. Understanding cerebellum contribution to PMS-associated phenotypes will allow development of new therapeutic strategies targeting the cerebellum in order to alleviate behavioural symptoms associated with this disease.

Disclosures: J. Archimbaud: None. **A. Sebold:** None. **J. Allégret-Vautrot:** None. **N. Heck:** None. **T. Bourgeron:** None. **D.A. DiGregorio:** None. **C. Rochefort:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.09/N15

Topic: H.08. Learning and Memory

Support: NIH Grant 1R21NS131634 (NINDS)

Title: Frataxin as an emerging target for the prevention of neuroaxonal injury and cognitive dysfunction in sickle cell disease

Authors: *R. HAZRA[1], S. LENHART[1], L. M. FOLEY[1], S. GHOSH[1], H. WANG[1], T. K. HITCHENS[2], S. CHAN[1], X. HU[3], E. NOVELLI[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurobio., Univ. of Pittsbrugh, Pittsburgh, PA; [3]Neurol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cerebrovascular white matter lesions and cognitive impairment are serious complications of sickle cell disease (SCD). The mechanism for the development of neuroaxonal damage leading to cognitive impairment in SCD is unknown. Astrocytes serve as a neurovascular physiological interface between the cerebral microvasculature and neurons. We reported that microstructural white matter injury, identified by diffusion tensor imaging (DTI) and immunohistopathology, is associated with activation of astrocytes in SCD mice (SS) homozygous for human hemoglobin S. Simultaneously, the SS mice displayed poorer cognitive function compared to control mice (AA), homozygous for human hemoglobin A. The cognitive

ability in the SS mice was strongly associated with the extent of white matter injury and astrocyte activation. Reduced expression of frataxin (FXN), a mitochondrial protein, is associated with deregulation of calcium signaling and cognitive impairment. We found lower astrocytic FXN expression in SS than in AA. We hypothesized that inhibition of FXN activates astrocytes and exacerbates neuroaxonal damage and cognitive impairment in SCD. We generated tamoxifen inducible astrocyte specific FXN knockout mice (FXN-KO) by crossing FXN-floxed mice with *Aldh1l1*-Cre mice. The FXN-KO and the wild-type (FXN-WT) mice were then transplanted with SS bone marrow to generate sickle chimeric mice, $SS^{FXN\text{-}KO}$ and $SS^{FXN\text{-}WT}$respectively with SCD phenotypes similar to the SS mice. The $SS^{FXN\text{-}KO}$, however, had worse cognitive response in the functional Y-maze ($n=12$; $p<0.05$) and novel object recognition ($n=12$; $p<0.01$) tests compared to the $SS^{FXN\text{-}WT}$. Ex-vivo DTI of the brains showed significantly reduced fractional anisotropy ($n=6$, $p<0.001$), an indicator of white matter injury. Immunofluorescence staining of the brain tissue showed substantial elevation in non-phosphorylated neurofilament H (SMI32) with a concomitant decrease in myelin basic protein (MBP) in $SS^{FXN\text{-}KO}$ mice ($n=6$; $p<0.05$). The increased ratio of SMI32/MBP indicated intensified neuroaxonal damage in $SS^{FXN\text{-}KO}$ mice. Increased astrocyte activation, indicated by the number of glial fibrillary acid protein expressing (GFAP+) astrocytes, was more pronounced in $SS^{FXN\text{-}KO}$ mice as compared to the $SS^{FXN\text{-}WT}$ mice ($n=6$; $p<0.01$). These data suggest that FXN is critical for regulating neuroaxonal health and cognitive function in SCD mice. This study introduces an innovative mechanism of cognitive impairment in SCD that underscores the role of astrocytic FXN activity in inducing white matter lesions. Induction of FXN may be developed as a therapeutic strategy to target cerebrovascular complications in SCD.

Disclosures: R. Hazra: None. **S. Lenhart:** None. **L.M. Foley:** None. **S. Ghosh:** None. **H. Wang:** None. **T.K. Hitchens:** None. **S. Chan:** None. **X. Hu:** None. **E. Novelli:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.10/N16

Topic: H.08. Learning and Memory

Support: NIH Grant R01 AG074012

Title: Genetic and sex differences pinpoint putative gene region in the relationship between glucose metabolism dysfunction and cognitive decline

Authors: *E. LITKOWSKI[1], A. R. DUNN[2], Y. DAI[3], Y. WU[4], T. J. HOHMAN[5], D. A. BENNETT[6], K. M. S. O'CONNELL[2], D. BRIDGES[1], C. C. KACZOROWSKI[7];
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Abstract: Diabetes and dementia have an unexpectedly high rate of comorbidity. However, the healthcare burden of these diseases differs by race/ethnic backgrounds (higher in non-Hispanic Black individuals) and by biological sex (higher in men for diabetes but women for dementia). To clarify the mechanism by which diabetes increases risk for cognitive decline, we utilized the Alzheimer's Disease BXD panel (AD-BXD), a mouse model incorporating genetic diversity with dominant mutations associated with early onset AD. Using a systems genetics approach, we studied 618 female and male mice (39 AD-BXD strains, and their non-transgenic littermate controls) fed either a low-fat chow diet or a high-fat, high-sucrose diet (HFHS) until 14 months of age. We evaluated their glucose metabolism through an intraperitoneal glucose tolerance test and their cognition utilizing a contextual fear conditioning assay. We found a relationship between an increase in peak glucose (15 minutes after glucose injection in fasted mice) and a decrease in cognitive function in AD females on a HFHS diet from 6 to 14 months of age. This measure explained 21% of the variance in cognitive decline in a sex-specific relationship not observed in males under the same conditions. Though the glucose measure did not reach a level of diagnosed diabetes, we mapped a quantitative trait locus (QTL) for the change in peak glucose on chromosome 9. In this locus, based on impact scores published in ENSEMBL Version 111, we prioritized *Prdm10,* a member of the positive regulatory domain. This family is characterized by an N-terminal PR domain followed by Zn-Finger repeats of variable length thought to enable interactions with other sections of the genome. The genetic region containing *PRDM10,* the human ortholog, has been implicated in genome-wide association studies of type 2 diabetes and diabetes complications and is associated with phosphorylated tau in SNP x SNP interactions with *TENM3* and *KL* in human studies. Additionally, we found that increased *PRDM10* gene expression was associated with lower cross-sectional cognition, faster cognitive decline, and greater tau tangle pathology in the caudate nucleus in the Religious Orders Study/Rush Memory and Aging project (ROSMAP). Our next step is to generate and breed mouse models to over- and under-express *Prdm10* in AD-susceptible female mice and test them on a HFHS diet across the lifespan. This assessment of the causal role of *Prdm10* will inform precision medicine therapies for individuals predisposed to diabetes and dementia.

Disclosures: E. Litkowski: None. **A.R. Dunn:** None. **Y. Dai:** None. **Y. Wu:** None. **T.J. Hohman:** None. **D.A. Bennett:** None. **K.M.S. O'Connell:** None. **D. Bridges:** None. **C.C. Kaczorowski:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.11/N17

Topic: H.08. Learning and Memory

Title: Effect of chronic unpredictable mild stress on learning and memory functions in C57BL/6 mice

Authors: *C. LEE, J.-H. JANG;
Sch. of Med., Keimyung Univ., Daegu, Korea, Republic of

Abstract: Stress affects the condition of the body and mental health, resulting in the occurrence of various physiological and psychological diseases that lead to learning and memory impairment. In this study, we evaluated the effect of chronic unpredictable mild stress (CUMS) on learning and memory function. The mice were exposed to CUMS, with or without social isolation (SI), for 4 weeks in C57BL/6 mice. To measure learning and memory function, the open field test (OFT), Y-maze test (YMT), and fear conditioning test (FCT) were conducted. CUMS led to learning and memory impairment compared with the normal group, which was further aggravated by SI. To elucidate the underlying molecular mechanisms, we have examined the molecules related to oxidative stress and neuroinflammation. The CUMS group exhibited increased oxidative stress, as evidenced by elevated levels of lipid peroxidation and decreased expression of antioxidant enzymes. Moreover, the levels of inflammation-related proteins, such as IL-1β, IL-6, IL-17 and TNF-α, were markedly up-regulated in CUMS-exposed mice. These findings suggest that CUMS may contribute to cognitive impairment by causing oxidative stress and inflammation in C57BL/6 mice.

Disclosures: C. Lee: None. **J. Jang:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.12/N18

Topic: H.08. Learning and Memory

Support: NIA R21 AG068444
NIA R01 AG074041
Hevolution-AFAR HEV-NI23020

Title: Age-related memory updating impairments linked to reduced engram overlap and transcriptional changes in the dorsal hippocampus

Authors: *C. A. BRUNSWICK, J. L. KWAPIS;
Penn State Univ., University Park, PA

Abstract: Memories are malleable and can be updated in response to new information. Deficits in memory updating are common with age-related cognitive decline and various dementias, but the mechanisms underlying these deficits are poorly understood. Here, we explore mechanisms for age-related memory updating impairments at both the cellular and transcriptional levels, using the Objects in Updated Locations (OUL) task to model a qualitative memory update in young adult (3-m.o.) and old (18-m.o.) C57BL/6J mice. We investigated engram dynamics during updating, hypothesizing that old mice do not properly coallocate the update engram with the initial training engram (i.e., they encode the update in different cells than those used for the

initial training). Using *Arc* catFISH in CA1 of the hippocampus, we first confirmed that old mice exhibit reduced coallocation (overlap) during updating relative to young mice. Next, we explored if increasing coallocation in old mice—biasing the storage of the update information into the engram used to store the initial training—would improve memory updating in old mice, using two different approaches. In the first approach, we expressed an excitatory DREADD in a small proportion of neurons in CA1. Then, we activated these cells during the OUL training sessions and the update session. As excitable neurons are preferentially recruited to memory engrams (Yiu et al., 2014), the DREADD-expressing neurons should be recruited to both the training and update engrams. In the second approach, we presented the OUL update session shortly after the final training session as prior work (Cai et al., 2016) has demonstrated that memories formed close together in time become coallocated. We found that increasing coallocation via either chemogenetics or our behavioral strategy alleviated memory updating impairments in old mice. Ongoing experiments are investigating transcriptional differences in the hippocampus of young and old mice following a memory update. Future experiments will track engram dynamics in OUL with a viral TetTag system that enables persistent expression of a fluorescent reporter in the original training engram.

Disclosures: C.A. Brunswick: None. **J.L. Kwapis:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

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Topic: H.08. Learning and Memory

Support: NIH NINDS SCORE-SC2NS119144
NIH NIGMS RISE R25GM110513
COBRE Seeds 5P20GM103642
Title V Grant Award #P031S160068

Title: Molecular Insights into Gender Differences in Gulf War Illness Pathology

Authors: *J. MARRERO, II[1], D. PEREZ[3], E. L. TOSADO RODRIGUEZ[4], A. ROCHE[5], P. A. FERCHMIN[6], N. SABEVA[2];
[1]Univ. Central Del Caribe, San Juan, PR; [2]Dept. of Neurosci., Univ. Central Del Caribe, Bayamon, PR; [3]Biochem., Univ. Central del Caribe, Bayamon, PR; [4]CCRHD-RCMI, [5]Univ. of Puerto Rico, MSC, San Juan, PR; [6]Neuroprotection For Life, Carmel, IN

Abstract: Gulf War Illness (GWI) is a chronic multi-organ condition primarily affecting the central nervous system (CNS) and is characterized by neuroinflammation, neuronal loss and behavioral/cognitive impairments such as memory deficits and anxiety. Exposure to Gulf War Illness-Related Chemicals (GWIRC) induces molecular and morphological changes in the brain of affected veterans. However, the critical molecular contributors linking GWIRC to chronic

neuroinflammation and neurological symptoms remain unclear. Recently, we demonstrated that male and female mice exhibit anxiety-like behavior and learning and memory impairments after being exposed to GWIRC. In this study, we identified molecular markers associated with learning and memory, neuroinflammation, and resting membrane potential in the hippocampus of male and female mice following exposure to GWIRC.
To recreate GWI conditions, we subjected C57BL/6J male and female mice to a GW-like exposure period consisting of either vehicle or a combination of the GWIRC, along with moderate stress. Long-term molecular alterations were evaluated through SDS-PAGE immunoblots conducted 8 months post-exposure. Our findings reveal sex-dependent disparities in the response to GWI-like conditions. Male GWI-afflicted mice exhibited reduced levels of hippocampal Alpha4-Beta2 (α4β2) nicotinic acetylcholine receptors (nAChR), a protein involved in cognitive processes such as learning and memory. In contrast, this effect was not observed in female counterparts. Additionally, male GWImice showed diminished levels of Inward rectifying potassium channel (Kir7.1), crucial for maintaining neuronal resting membrane potential, indicating potential alterations in neuronal excitability, contrasting with the unchanged levels observed in females. Notably, female GWI-affected mice exhibited elevated levels of glial fibrillary acidic protein (GFAP) compared to control females. In contrast, male GWI-mice did not display significant differences in GFAP levels compared to controls, but did exhibit decreased levels of CD45, a protein implicated in the suppression of microglial activation, suggesting dysregulated microglia response.
These results indicate that α4β2, Kir7.1, and astrocyte hypertrophy and activated microglia play pivotal roles as mediators of the persistent cognitive and behavioral deficits, as well as neuroinflammation, evident in GWI. Moreover, these findings offer novel insights into the sex-specific differences within this model, thereby enriching our understanding of GWI pathology.

Disclosures: J. Marrero: None. **D. Perez:** A. Employment/Salary (full or part-time):; Laboratory technician. **E.L. Tosado Rodriguez:** 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.; Integrated Informatics Services Facility to the UPR. **A. Roche:** 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.; Integrated Informatics Services Facility to the UPR. **P.A. Ferchmin:** None. **N. Sabeva:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.14/N20

Topic: H.08. Learning and Memory

Support: NIH Grant AG062398

Title: Hippocampal expression of eukaryotic translation initiation factor 4E binding protein 2 (4EBP2) alters behavior differently in females compared to males

Authors: S. P. FEENEY[1], J. M. MCCARTHY[1], S. BORRELLO[1], C. DENNIS[1], D. VO[1], W. DANKER[1], *J. C. TUDOR[2];
[2]Biol., [1]St. Joseph's Univ., Philadelphia, PA

Abstract: Sleep loss produces deficits in protein synthesis that lead to impaired hippocampus-dependent memory storage. The protein synthesis required for memory formation is dependent on several signaling pathways, one of which includes mammalian target of rapamycin (mTOR) and eukaryotic initiation factor 4E-binding protein 2 (4EBP2). Previously, we determined that the estrous cycle in intact female mice does not affect mTOR activity under control conditions. However, five hours of acute sleep deprivation significantly reduced mTOR activity and protein synthesis in the hippocampus of female mice. Additionally, we found that spatial memory, as measured in the object place recognition task, is significantly impaired in both sexes following 5 hours of acute sleep deprivation by gentle handling. It was yet to be determined, however, whether restoring protein synthesis in the hippocampus is sufficient to prevent the cognitive deficits associated with sleep deprivation. Here, we developed a mutant phosphomimetic 4EBP2 AAV that prevented memory impairments associated with sleep deprivation, and a phosphodefective 4EBP2 AAV that did not rescue memory impairments induced by sleep deprivation. Interestingly, the expression of mutant 4EBP2 in the hippocampus of female mice increased the prevalence of some behaviors in the zero maze task. Overall, though the estrous cycle does not significantly affect mTOR activity under control and sleep deprivation conditions, mutant 4EBP2 AAV expression in the hippocampus does affect the behavior of females differently compared to males. This underscores the need for continued research examining how males and females are differentially affected by sleep loss and its subsequent impact on cognition.

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Poster

PSTR139: Molecular Mechanisms of Memory

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Program #/Poster #: PSTR139.15/Web Only

Topic: H.08. Learning and Memory

Support: Departamento de Ciencias de la Salud
Consejo Mexiquense de Ciencia y Tecnología
FPIS-INCAN-4352/Ministry of Health Mexico

Title: Analysis of sensorimotor stimulation as a neuroprotective strategy in a model of cognitive impairment induced by a high-calorie diet.

Authors: *S. HERNÁNDEZ-RAMÍREZ[1], S. RUIZ-PÉREZ[3], M. TRUJILLO[3], K. TORRES[3], P. SALCEDO[4], R. GONZALEZ BARRIOS[3], K. R. GUZMAN-RAMOS[2];
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Abstract: Chronic intake of a high-calorie diet has been shown to decrease cognitive capacity in humans and animal models. Thus, effective pharmacological and non-pharmacological strategies are being investigated to prevent or ameliorate the harmful effects of consuming high-calorie diets. In this regard, Environmental Enrichment (EE) is a non-pharmacological approach that significantly improves synaptic plasticity and brain function. EE is characterized by brain stimulation through the enhancement of sensory and motor skills, which in the long-term will improve the learning and memory. Complex designs of EE include exercise wheels or items to increase physical activity; hence, the beneficial effects of EE could be attributable to a combination of environmental factors. The aim of this study was to assess the effect of sensorimotor stimulation without an increase in physical activity on the cognitive performance of a murine model of diet-induced cognitive impairment. We studied C57BL/6 male mice fed with a high-fat and high-fructose diet (HCD; 60% fat, 10% fructose) or normal chow for 26 weeks, concomitantly exposed to either novel objects, that were every fourth day, or to a regular housing. Afterwards, spatial memory and metabolic characteristics were evaluated: NC-NE (normal chow, non-enriched, n= 9); NC-EE (normal chow, enriched, n= 9); HCD-NE (high-calorie diet, non-enriched, n= 9) and HCD-EE (high-caloric diet, enriched, n= 6). Our results indicate that constant novelty in the EE setup prevents the spatial memory decline showed by the HCD animals on regular housing. HCD did not modify weight gain, however, the metabolic impact of HCD diet was evident in larger fat accumulation, higher levels of fasting glucose and lower glucose tolerance compared to NC animals. This shows that specific cognitive stimulation provides protective benefits even in the presence of metabolic dysfunction. Moreover, to understand the underlying mechanisms of functional preservation, we used a high-throughput sequencing essay (RNA-seq) to assess gene-expression changes in the hippocampus of the experimental groups. We found that diet and enrichment suppress genes involved in mitochondrial processes like oxidative phosphorylation and activate genes associated with axonogenesis and synaptic organization. These findings may have profound implications for our understanding of the beneficial effects of EE over cognitive health and potential interventions.

Disclosures: S. Hernández-Ramírez: None. **S. Ruiz-Pérez:** None. **M. Trujillo:** None. **K. Torres:** None. **P. Salcedo:** None. **R. Gonzalez Barrios:** None. **K.R. Guzman-Ramos:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.16/N21

Topic: H.08. Learning and Memory

Support: NIA Grant K01AG066847
NIA Supplement Grant GR1063343

Title: Laminar organization of neuronal cell types defines distinct CA1 hippocampal subregions

Authors: *M. PACHICANO, S. MEHTA, Z. SMITH, A. HURTADO, M. S. BIENKOWSKI; Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA

Abstract: Characterization of neuronal cell types in highly integrated neuroanatomical structures such as hippocampal CA1 is critical to determine the cellular mechanisms underlying cell type susceptibility in neurodegenerative diseases. Transcriptomics techniques revealing single molecule gene expression with single cell resolution have advanced our understanding of CA1 cell-type diversity. However, the overall organization of CA1 cell types and their spatial organization along the hippocampal longitudinal axis remains unclear. A previous study using single cell RNA-seq described a gradient organization of CA1 cell types (Cembrowski et al, 2016), while another study using Seq-FISH spatial transcriptomics described CA1 subregions composed of a cellular mosaic (Shah et al, 2016). More recent spatial transcriptomics studies reveal gradient formation of glutamatergic cell types in CA1 (Yao et al, 2021), yet consensus on this topic remains elusive.Our previous work creating the mouse Hippocampus Gene Expression Atlas (HGEA) defined cell types based on connectivity and gene expression, revealing specific marker gene expression patterns in CA1 neuronal cell- types (Bienkowski et al, 2018). We hypothesized that these CA1 gene expression patterns reflected a hidden laminar organization, similar to those observed in the subiculum but were difficult to distinguish. Electrophysiological differences between deep and superficial layers of dorsal CA1 pyramidal cells has been demonstrated previously (Valero et al, 2015) but comprehensive CA1 cell type laminar organization is unknown. In this study, we used RNAscope single molecule fluorescent in situ hybridization (smFISH) to label HGEA marker genes and quantify individual RNA transcript levels within CA1 cell types along the hippocampal axis. 20μm thick coronal C57Bl/6 mouse brain sections were hybridized with probes targeting CA1 gene expression markers using RNAscope HiPlex V2 kit (Advanced Cell Diagnostics). Sections were counterstained for DAPI cytoarchitecture, imaged at 40X, and analyzed using QuPath (Quantitative Pathology and Bioimage Analysis) and SCAMPR software (Ghoddousi et al, 2022). RNAscope labeling produced robust datasets enabling quantification of single RNA transcript levels for each gene expression in 20,000+ CA1 cells. We found that our previously described HGEA CA1 subregions can be re-defined as multiple distinct cell type specific layers. These cell type specific lamina within CA1 subregions indicate functional heterogeneity that can provide valuable insights into CA1 cell type vulnerability in neurodegenerative diseases as well as potential therapeutic targets.

Disclosures: M. Pachicano: None. **S. Mehta:** None. **Z. Smith:** None. **A. Hurtado:** None. **M.S. Bienkowski:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.17/N22

Topic: H.08. Learning and Memory

Support: NIDA U01DA051972

Title: The role of CASK in the regulation of neuronal activity-dependent gene transcription and memory

Authors: *A. M. LIBSTER[1], P. MONTILLA-PEREZ[2], A. KUMAR[2], Y. MENG[3], S. DESFOR[2], F. MALHOTRA[2], N. CASTORENA[2], F. TELESE[2];
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Abstract: Neuronal activity-regulated gene (ARG) transcription is critical for learning and memory and is attributed to the precision of experience-dependent gene expression programs. However, the underlying gene regulatory mechanisms are not completely understood. In this study, we characterized the role of calcium/calmodulin-dependent serine protein kinase (CASK) in transcriptional mechanisms driving ARG expression The knock-down of CASK in the mouse hippocampus resulted in impaired expression of the neuronal activity-dependent gene, Fos, following foot shocks and reduced novel object recognition in the six different objects paradigm. Using primary cultures of cortical neurons before and after membrane depolarization triggered by elevated KCl levels, we found that the localization of CASK in the nuclear and chromatin-bound fractions was independent of KCl treatment. However, neuronal activity increased the binding of CASK by ChIP-seq to cis-regulatory elements in the proximity of ARGs. CASK binding positively correlated with the signal-dependent occupancy of RNA polymerase II transcriptional machinery, suggesting that CASK acts as a transcriptional co-activator. The knockdown of CASK reduced the activation of ARGs expression by RNA-seq and associated enhancer RNAs mapped by capped small (cs)RNA-seq. De novo motif analysis indicated that the loss of CASK altered the temporal dynamics of transcription factors activity in response to neuronal activity, such as CREB and AP1. These findings offer novel insight into molecular mechanisms underlying ARG expression and memory formation.

Disclosures: A.M. Libster: None. **P. Montilla-Perez:** None. **A. Kumar:** None. **Y. Meng:** None. **S. Desfor:** None. **F. Malhotra:** None. **N. Castorena:** None. **F. Telese:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.18/N23

Topic: H.08. Learning and Memory

Support: NIH P20GM103423

Title: Tet Enzyme Degrader Modifies DNA Methylation in the Hippocampus and Enhances Long-Term Memory

Authors: A. REARDON[1], E. BARNES[1], *A. KENNEDY[2];
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Abstract: Active DNA methylation in neurons recruited by experiential learning is required for long-term memory formation. TET enzymes oxidize and lead to the removable of DNA cytosine methylation, functioning as epigenetic erasers. Here we demonstrate that the conditional knockout of Tet2 in glutamatergic neurons induces enhanced long-term memory retention in mice at spatial memory tasks. Additionally, the IP administration of the TET enzyme degrader, Bobcat339, was sufficient to penetrate the brain and enhance long-term spatial memory, but variably based on task and age. Whole genome bisulfite sequencing was used to detect loci of altered DNA methylation induced by TET enzyme deletion and degradation. These data suggest that the TET enzymes are negative regulars of memory retention in neurons by regulating the expression of plasticity-related genes and are a target for memory enhancement.

Disclosures: A. Reardon: None. **E. Barnes:** None. **A. Kennedy:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.19/N24

Topic: H.08. Learning and Memory

Title: Regulation of hippocampal transcription and memory formation by the atypical histone variant mH2A1 is splice isoform-specific

Authors: *T. A. B. MCLEAN[1], S. CREIGHTON[2], G. STEFANELLI[3], M. A. BRIMBLE[4], A. LEONETTI[5], B. J. WALTERS[6], I. B. ZOVKIC[2];
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Abstract: The formation of long-lasting memories requires learning-induced changes in gene expression. Basal levels of inducible genes are tightly regulated by epigenetic factors, including histone variant deposition, that modulate DNA accessibility and transcription factor binding. Although a role for post-translational modification of canonical histones in memory is well-established, histone variants were only recently identified as epigenetic regulators of memory, with functional roles described for the variants H2A.Z and H3.3. Our lab recently characterized macroH2A1 (mH2A1), a structurally unique H2A variant bearing a large non-histone

macrodomain, as another novel regulator of memory. Hippocampal depletion of mH2A1 induces widespread de-repression of hippocampal transcription and impairs hippocampal-dependent memory in mice. Here, we investigate the molecular and mechanistic basis of these mH2A1 phenotypes by assessing the function of the mH2A1 splice isoforms mH2A1.1 and mH2A1.2, which bear structurally distinct macrodomains. Only the macrodomain of mH2A1.1 binds poly(ADP)-ribose (PAR) and inhibits activity of poly(ADP-ribose)polymerase 1 (PARP1), a nuclear protein which positively regulates memory formation and activity-dependent neuronal transcription. We find that selective knockdown of mH2A1.1 or mH2A1.2 produces distinct transcriptional outcomes and behavioral phenotypes, with mH2A1.1 knockdown blocking activity induction of IEG expression *in vitro* and impairing long-term contextual fear memory consolidation in mice. Moreover, co-depletion of PARP1 reduces basal expression of a subset of mH2A1.1-regulated IEGs and rescues impaired fear memory in mH2A1.1 knockdown mice. We also find distinct genes dysregulated in the mouse hippocampus by knockdown of mH2A1.1 or mH2A1.2. These studies are the first to characterize the functional relevance of PARP1-macrodomain interactions in transcription and memory formation. We propose that mH2A1.1-specific regulation of *PARP1* expression and PARP-1 activity is a major mechanism by which mH2A1 regulates neuronal transcription and memory formation.

Disclosures: T.A.B. McLean: None. **S. Creighton:** None. **G. Stefanelli:** None. **M.A. Brimble:** None. **A. Leonetti:** None. **B.J. Walters:** None. **I.B. Zovkic:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

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Program #/Poster #: PSTR139.20/N25

Topic: H.08. Learning and Memory

Support: Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery grant 2021-02926 to C.T.D.

Title: Intra-amygdalar infusions of either muscimol or anisomycin produce equivalent memory impairments on cued and contextual fear memories

Authors: *S. AL-SMADI[1], M. SAINI[2], L. A. RIMSTAD[3], C. T. DICKSON[4];
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Abstract: Memory consolidation is thought to rely on the synthesis of new proteins, a conjecture supported by behavioral experiments using protein synthesis inhibitors (PSIs). PSIs such as anisomycin, cycloheximide, and emetine, have been shown to disrupt long-term memory when infused shortly after training. However, these same substances catastrophically suppress neural activity when applied. Thus, memory consolidation may actually be reliant on neural activity in the post-learning period. In this study, we compare the effects of intra-amygdalar applications of

anisomycin to the GABAergic agonist muscimol in cued and contextual fear conditioning paradigms. Using male SD rats, guide tubes were implanted bilaterally to both amygdalae. Following standard fear conditioning, rats were bilaterally infused with anisomycin, muscimol, or PBS and both cued and contextual retention tests were conducted 48 hours afterwards. Our results showed that both anisomycin and muscimol groups exhibited significantly reduced freezing behavior compared to the control group, with no notable differences between them. These findings suggest that the disruption in behavior observed following anisomycin infusion is not solely attributable to a reduction in plasticity-related proteins but rather via the suppression of neural activity. This study highlights the importance of considering the broader effects of PSIs on neural function when interpreting their impact on memory consolidation.

Disclosures: S. Al-Smadi: None. **M. Saini:** None. **L.A. Rimstad:** None. **C.T. Dickson:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.21/N26

Topic: H.08. Learning and Memory

Support: NIH R01-HD103888
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Title: Stra8: A Novel Activity-Dependent Modulator of Neural Circuits

Authors: *M. HUANG, N. WANG;
The Univ. of Kansas, Kansas City, KS

Abstract: Neural circuits rely on activity-dependent modulators to mitigate excitotoxicity during neuronal activity, safeguarding neurons from internal harm. In this study, we identified that *stimulated by retinoic acid gene 8* (*Stra8*), previously considered specific to germ cells, acts as a novel modulator in neural circuits. Our results, using qPCR, Western blot analysis, and immunofluorescent staining, demonstrate that a 2-hour exposure to a novel environment significantly induced Stra8 expression in neuronal cells in adult mouse brains. Moreover, *in vitro* studies using primary hippocampal neurons show that N-methyl-D-aspartate (NMDA) stimulation induced Stra8 expression within 2 hours, reaching its peak at 10 hours and subsequently declining by 24 hours. Conditional knockout of *Stra8* in neuronal cells by nestin-Cre (*Stra8*$^{f/-}$;nestin-Cre; *Stra8*-cKO) in mice significantly increased their vulnerability to kainic acid (15 mg/kg)-induced excitotoxicity, resulting in uncontrolled seizures and a 100% mortality rate within 10 hours. Further examination of *Stra8*-cKO mice shows a reduction in the inhibitory neurotransmitter enzyme, glutamate decarboxylase 67 (GAD67). Cognitive function assessments using Barnes maze test show that *Stra8*-cKO mice (n=12) exhibit significant impairment in

spatial learning and memory compared to controls (n=9), with longer latencies (*P*=0.001635) but comparable velocity. Additionally, neurons in *Stra8*-cKO mice brains exhibited disrupted proteostasis characterized by the accumulation of protein aggregates and autophagosomes, genomic instability evidenced by increased DNA double strand breaks (DSBs) detected by γH2AX and heterochromatin detected by H3K9me3, and elevated levels of lipofuscin, a marker of aging. Transcriptomic analysis of Stra8-expressing cells from hippocampi of wild-type and *Stra8*-deficience mice by RNA-seq highlights upregulation of synaptic signaling genes, including *Vgf* (*VGF nerve growth factor inducible*) and *Npas4* (*neuronal PAS domain protein 4*), and downregulation of stimulus-responsive genes, such as *Pvalb* (*parvalbumin*). Chromatin immunoprecipitation and sequencing (ChIP-seq) in mice expressing Avi-tagged Stra8 demonstrates significant occupancy of Stra8 at the regulatory sequences of the *Npas4* and *Vgf* genes. Collectively, our study identifies Stra8 as a novel activity-dependent modulator of neural circuits, contributing to neuronal protection by regulating key genes involved in synaptic structure and activity.

Disclosures: M. Huang: None. **N. Wang:** None.

Poster

PSTR139: Molecular Mechanisms of Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR139.22/N27

Topic: H.08. Learning and Memory

Support: Shanghai Municipal Commission of Science and Technology Program

Title: The epigenetic mechanisms of remote memory impairments in the Kabuki syndrome mouse model

Authors: *W. LI, Y. LI;
Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Kabuki syndrome (KS) is a rare disease that mainly manifests as congenital developmental abnormalities and mental disorders, with a prevalence of approximately one case in 32,000 newborns. Utx, a Histone demethylase, is a pathogenic gene in KS. While intellectual disability is a prominent feature of Kabuki syndrome, the role of Utx in cognitive function has been unclear. Here, we found that Utx knockout mice showed disrupted calmodulin transcription and cognitive deficits. Importantly, these deficits were ameliorated by desipramine, suggesting a potential therapeutic approach for Kabuki syndrome through the modulation of Utx's epigenetic mechanism. More interestingly, the Utx KO mice showed remote memory impairment. To delve deeper into this matter, we examined the engram cells at the pivotal stage of learning and memory, mapped the brain-wide reconstruction of engrams, and investigated the dynamic changes of histone methylation in contextual fear memory. The findings will shed the light on the mechanisms of the retention of remote memory.

Disclosures: W. Li: None. **Y. li:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.01/N28

Topic: H.09. Spatial Navigation

Support: Marge und Walter Boll-Stiftung grant 210-05.01-21

Title: Cortical dynamics underlying cognitive strategies in human wayfinding decisions

Authors: *J.-Y. HUANG[1], O. L. BOCK[1], D. MEMMERT[1], O. ONUR[2];
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Abstract: Finding our way in a city or building requires us to decide which direction to take at intersections. Five cognitive strategies have been identified that could be used for such decision-making. In a recent study, we asked participants to find their way through five strategy-specific virtual mazes, and found evidence for strategy-specific mechanisms (Bock et al., 2024). The present study aimed to examine this behavioral finding at a neuronal level. For this, young adults were asked to find their way through five strategy-specific virtual mazes, and their cortical activity was measured using a 64-channel EEG system with ActiChamp Plus amplifiers. The first trip through each maze was externally guided, and the subsequent five trips were self-guided. Independent component analysis was applied to reveal clusters and to identify the patterns of brain activity underlying each strategy. We found activity related to correct wayfinding decisions in the frontal, parietal, temporal, occipital, and limbic lobes. Importantly, the pattern of specific absolute spectral power in those clusters, and their connectivity, varied between the strategy-specific mazes. From this, we conclude that different decision-making strategies were associated with different processing demands across several brain regions.

Disclosures: J. Huang: None. **O.L. Bock:** None. **D. Memmert:** None. **O. Onur:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.02/N29

Topic: H.09. Spatial Navigation

Support: Research Council of Norway Young Research Talents Award 274328

Title: Dynamic representations of tactile cues and spatial location in RSC neurons over the course of learning

Authors: C. N. BERGE[1], N. LENKEY[2], W. GUO[3], E. HENNESTAD[4], K. VERVAEKE[1], ***A. R. CHAMBERS**[5];
[1]Univ. of Oslo, Oslo, Norway; [2]Mol. Med., Univ. of Oslo, Oslo, Norway; [3]The Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [4]Basic Med. Sci., Univ. of Oslo, Oslo, Norway; [5]Harvard Med. Sch., Boston, MA

Abstract: The retrosplenial cortex (RSC) is a key hub for spatial processing—it is sensitive to spatial features such as head direction, and displays place cell-like tuning. RSC neurons also respond to external sensory variables such as visual and tactile cues, and internal brain state events such as sharp-wave ripple (SWR) oscillations. Recent studies indicate that RSC sensitivity to spatial, sensory, brain state and behavioral variables are not necessarily fixed and predetermined, but can show dynamic, context-dependent properties. To explore this, we asked whether tuning to external or internal events was stable over consecutive days within and across a spatial task where rewards were randomly distributed or fixed. We performed repeated head-fixed two-photon calcium imaging of the same neural populations using GCaMP8 in RSC layer 2/3 before, during and after mice performed tasks on a wheel with fixed tactile cues. LFP electrodes in hippocampal CA1 recorded sharp-wave ripples (SWR). Each mouse performed two task configurations: (1) a random foraging task on a wheel with tactile cues, with randomly located water rewards (**RF**), and (2) a goal-oriented task where the tactile cues were unchanged, but the reward location was fixed (**GOL**). On each day, "offline" recording sessions were performed before and after the behavioral task as the animal sat passively on a disk. Although the wheel and tactile cues were the same between the RF and GOL tasks, the reward configuration significantly altered neural representations in RSC and SWR occurrence rate in CA1. In CA1, when comparing “offline” recording sessions, the SWR occurrence rate was significantly higher in the post-behavior session than the pre session, but only for GOL task days. In RSC, single neuron responsiveness to SWR events was largely stable over days. However, the distribution of cue and place tuning was significantly different depending on the task. Cue responses dominated in the RF task, while cellular tuning was predominantly related to place fields in the GOL task. Individual neurons could demonstrate stable tuning across behavioral conditions, could lose or gain tuning in the RF or GOL task, or could switch from multi-peaked cue tuning in the RF task to a single place field in the GOL task. The RSC population representation of space was notably less noisy in the GOL task, likely reflecting the increase in place-tuned neurons. In conclusion, tuning to cue or place appears to be strongly dependent on an anchored reward, and the same neurons can switch between sensory cue tuning and place field representations depending on the behavioral configuration of the task.

Disclosures: C.N. Berge: None. **N. Lenkey:** None. **W. Guo:** None. **E. Hennestad:** None. **K. Vervaeke:** None. **A.R. Chambers:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.03/N30

Topic: H.09. Spatial Navigation

Title: Systematic comparison of receptive field properties across a distributed egocentric vector cell circuit

Authors: *X. LIN, E. CIMINO, A. S. ALEXANDER;
Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Recent work has revealed spatially-tuned neurons with receptive fields that are sensitive to egocentric bearing and/or distance to environmental features such as boundaries/centers, landmarks, and goals. Neurons with this form of egocentric tuning have now been reported in numerous cortical and subcortical regions including dorsal striatum, retrosplenial, parietal, secondary motor, lateral entorhinal, and postrhinal cortices. The distributed nature of this signal amongst strongly interconnected regions suggests the possibility of a hierarchical processing scheme resembling that observed in the head direction system. A critical first step in revealing dependencies between regions possessing this form of egocentrically tuned neuron requires comparison of receptive field features and examination of co-activity patterns. Here, we analyze existing and new neurophysiological datasets in rats and mice to compare tuning strength, field distributions, stability, and multiple other properties of egocentric bearing and distance tuned neurons recorded from multiple neocortical association regions. We also examine spike timing relationships of simultaneously recorded egocentric bearing and distance tuned cells in densely interconnected retrosplenial and posterior parietal cortices. We also perform inactivations to test circuit interactions between these two regions critical for the emergence of such receptive fields. These findings begin to unravel contingencies amongst a broad network of areas employing an egocentric vector based spatial code.

Disclosures: X. Lin: None. **E. Cimino:** None. **A.S. Alexander:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.04/N31

Topic: H.09. Spatial Navigation

Title: Spatial context invariant representations in the retrosplenial cortex

Authors: *E. CIMINO[1], X. LIN[1], A. S. ALEXANDER[2];
[1]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA;
[2]Psychological and Brain Sci., UC Santa Barbara, Santa Barbara, CA

Abstract: The retrosplenial cortex (RSC) is a midline association cortex that is essential to spatial cognition and navigation. RSC may have a unique role in mediating spatial coordinate transformations, which is supported by its reciprocal anatomical connections with structures representing spatial information either in egocentric or allocentric coordinate frames, such as posterior parietal cortex, parahippocampal regions, the hippocampus, and the anterior thalamic nuclei. RSC itself exhibits numerous forms of spatial responsivity including turn direction sensitivity, egocentric boundary vector tuning, head direction tuning, and landmark-dominated head direction coding. Many of these response fields have been characterized during either free foraging or maze running but have not been directly compared between spatial contexts. In order to explore this, we used in vivo electrophysiology to compare the same populations of retrosplenial neurons in both free foraging conditions and during track running alternation on a T maze within a single day. We found that spatial stability in one condition is predictive of the level of spatial stability in the other, suggesting the presence of a specialized sub-population of RSC neurons exhibiting spatial tuning. This invariant spatial stability was not solely restricted to neurons previously shown to exhibit context invariance, such as head direction or egocentric boundary vector cells (EBCs). During track running conditions, we observed that EBCs detected in the open field show punctate spatial receptive fields, primarily concentrated around turn locations. This unique nature of EBC receptive fields on the track enabled us to test for coordination of these neurons with the extended hippocampal formation via phase precession. This cross-task comparison of receptive field characteristics yielded important insights regarding the base tuning properties that define RSC functional phenotypes.

Disclosures: E. Cimino: None. **X. Lin:** None. **A.S. Alexander:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.05/N32

Topic: H.09. Spatial Navigation

Support: Sorbonne Université
Collège de France

Title: Communication between Hippocampus, Ventral Tegmental Area and Nucleus accumbens during learning and memory

Authors: *R. J. BRITO[1], M. ZUGARO[2];
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Abstract: The hippocampus is thought to form the brain substrate of a cognitive map. While the spatial component of this map involves hippocampal ‘place’ cells, non-spatial features may require coupling with other brain areas. This could involve ‘hippocampal sequences’,

endogenous activations of successive place cells representing entire trajectories at a highly accelerated rate. These sequences are paced by theta or ripple oscillations, and could participate in learning and memory, as well as goal-directed decision making. However, the association between hippocampal sequences and reward- and goal-related signals remains poorly understood. The ventral tegmental area (VTA) and nucleus accumbens (Nacc) are involved in reward coding and goal-directed action selection, and have both been independently reported to activate during hippocampal ripples. These co-activations could be part of a broader mechanism, whereby the three structures coordinate at a precise timescale during hippocampal oscillations, with different characteristics depending on cognitive function.
To explore these questions, we performed electrophysiological recordings from dozens of single units in the dorsal hippocampus, NAcc and VTA simultaneously, in rats trained to learn a complex spatial memory task in the 'Hippodamos maze': this novel task features a daily-changing set of reward and error zones, requiring the rats to learn elaborate spatial configurations, to flexibly adapt to changes in these configurations, and every day learn and remember trajectories never experienced before. We investigate how the hippocampus, NAcc and VTA coordinate during various cognitive functions (learning, recall, planning, long-term storage, etc.) and relate to the performance of the animals in the task.

Disclosures: R.J. Brito: None. **M. Zugaro:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

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Program #/Poster #: PSTR140.06/N33

Topic: H.09. Spatial Navigation

Support: ERC Grant NavigationCircuits 714642
ERC Grant MentalTravel 101087404

Title: Differential goal and state representations between prefrontal subregions during navigation

Authors: *C. SHEN, H. T. ITO;
Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Goal-directed navigation in a complex environment requires not only a precise estimate of the target location, but also a plan for navigational routes corresponding to a given spatial layout of the environment. While a recent study showed that neurons in the prefrontal cortex encode navigational goals (Basu et al., 2021), it has been reported that prefrontal neurons represent an animal's movement directions or routes (Ito et al., 2015), leading to a question of whether these neurons encode a goal and a route independently or conjunctively. To address this question, we designed a new maze in which an animal is required to take different routes to reach a given goal location, allowing us to isolate representations of goal and route.
Recording from neurons in the orbitofrontal cortex (OFC) while the rat performed this task

showed that these neurons pointed to the animal's subsequent goal destination at the beginning and this representation mostly persisted throughout the journey, regardless of its route choices. Notably, we found that the activity of the same OFC neural population additionally possessed the information of the animal's subsequent movement direction at the T-junction of the maze, and this action representation was embedded in a subspace orthogonal to that of goal coding. In trials where the animal made a wrong turn but immediately corrected this behavior without licking an incorrect well, we found that OFC neurons represented the action that could lead to the correct goal while forming a goal representation for the wrong destination, leading to a dissociation between goal and action representations. Optogenetic perturbation of OFC neurons significantly reduced this self-correcting behavior and increased incorrect well-lickings, suggesting a pivotal role of the OFC in goal recognition.
While the OFC's activity encodes the goals and actions of individual journeys in the task, we found that neurons in the medial prefrontal cortex (mPFC) contain distinct information reflecting the overall task structure. Corresponding to the task rule where animals must alternately target one of the two goals, the activity of mPFC neurons can differentiate these two alternation states during behaviors, categorizing individual journeys according to the alternation rule.
These results together suggest different contributions of the OFC and the mPFC in navigation - the OFC generates planning for the next immediate journey, whereas the mPFC captures the broader task structure, likely facilitating strategic goal decisions based on the task rules.

Disclosures: C. Shen: None. **H.T. Ito:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.07/N34

Topic: H.09. Spatial Navigation

Support: NIMH R01-MH101297
Hartwell Fellowship
NARSAD Young Investigator Grant
T32MH067564

Title: Reward experience coding in the lateral entorhinal cortex during goal-directed navigation

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Abstract: The hippocampus integrates information about where events occurred with what exactly occurred to form a cognitive map. The spatial information is represented by grid cells, border cells, and more in the medial entorhinal cortex, but the source and nature of experiential information, such as the anticipation and consumption of a reward, is less clear. Given that the

main source of inputs to the hippocampus is routed through the entorhinal cortex, we sought to investigate the relative contributions of its medial (MEC) and lateral (LEC) subdivisions during reward-based navigation. We trained mice in virtual reality to navigate to hidden moveable rewards, allowing us to dissociate the representations of spatial and experiential aspects of the behavior. We also developed surgical methods that enabled two-photon functional imaging of the LEC through an implanted microprism (Issa et al, 2024). We found a stark contrast between regions: while the MEC represented spatial position, as expected, it was the LEC that represented the reward itself. Moreover, these representations were specific to the experience of the reward, with largely separate and dedicated populations of neurons signaling goal approach, reward consumption, and goal departure. Optogenetic inhibition of LEC disrupted learning of a new reward location. Thus, the LEC provides the hippocampus reward-centric experiential information that contextualizes the spatial code found in the MEC, and this factorization may serve as a computationally efficient and flexible means for learning to associate these two components of episodic memory.

Disclosures: J.B. Issa: None. **B.A. Radvansky:** None. **F. Xuan:** None. **D.A. Dombeck:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Johns Hopkins University Discovery Award
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Ezoe Memorial Recruit Foundation Fellowship
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Title: Coupling and decoupling of place cells and head direction cells under conflicting frames of reference

Authors: *Y. SUEOKA[1,2], R. P. JAYAKUMAR[2,3], M. FERREYROS[2], B. Y. LI[2], M. S. MADHAV[2,3,4], X. CHEN[5], N. J. COWAN[3,6], J. J. KNIERIM[1,2,4];
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Abstract: Hippocampal place cells are part of an internal, cognitive map that is thought to guide spatial navigation. A key input to the place cell network is the allocentric direction signal from head direction (HD) cells. HD cells are strongly coupled to place cells under discrete rotations of distal visual landmark cues (Knierim et al., 1995; Yoganarasimha et al., 2005). Here, we investigate the extent of this coupling as animals experienced continuously conflicting frames of reference. We simultaneously recorded from place cells in dorsal CA1 and HD cells in the anterior dorsal thalamic nucleus and the retrosplenial cortex from five Long Evans rats (two male, three female). As animals ran around a circular track inside the Dome VR apparatus (Madhav et al., 2022) in pursuit of food reward, an array of visual landmarks was projected onto the interior of the Dome. After the first epoch, in which the landmarks were stationary in the lab frame, this array was rotated as a function of the rat's movement, dissociating the lab and the landmark frames. In 49/67 sessions, the hippocampal frame, as decoded from place cell activity, was anchored to the landmarks, i.e., place fields remained stable within the moving landmark frame of reference. Simultaneously recorded HD cells also maintained their tuning relative to the landmarks. In the remaining 18 sessions, both place cells and HD cells broke away from the visual cues and continuously drifted with respect to the landmark frame. The drift rate often settled to values in which the relationship between distance traveled in the hippocampal frame versus the landmark frame was described by a simple n:m ratio (where n and m were small integer values; Secer, Jayakumar, et al., SfN, 2023) for a variable number of laps, indicating stable periodic equilibria between competing landmark and lab frames. Regardless of the nature of the hippocampal map drift, place and HD cells were coherent in 16/18 sessions, demonstrating that these populations were tightly coupled even when the internal map lost its static association with the external world. Interestingly, in 2/18 sessions, we observed a split in the place cell population. While some place cells drifted along with the HD population, others only fired on occasions when the alignment of the drifting HD and landmark frames returned to their initial condition. This conjunctive coding meant that some place cells could be under the influence of HD cells despite a lack of 1:1 coupling between the two systems. In sum, our results demonstrate that the association of place and HD cells is maintained even under conflicting frames of reference, sometimes resulting in the dissociation of internal maps from the external world.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR140.09/N36

Topic: H.09. Spatial Navigation

Support: NIA P01 AG009973

Title: Lateral entorhinal cortex odor-place representations under context-dependent rule switches in young and aged Long-Evans rats

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Abstract: The entorhinal cortex is a key structure that mediates communication between the hippocampus and neocortex. Medial entorhinal cortex may comprise a context pathway, encoding allocentric space as the framework of experience, while lateral entorhinal cortex (LEC), holding the richest set of association connections in the rat cortex, may provide the content of an experience by representing local sensory information. During associative learning, LEC cells show increased cue selectivity necessary for successful odor-place retrieval (Igarashi et al., 2014) and develop overlapping representations of multiple rewarded odor cues, separated from unrewarded cues (Lee et al., 2021). However, items may reappear in distinct contexts and can be of different significance. The present study aims to understand whether and how LEC activity in response to identical cues is flexibly reconfigured to support successful retrieval of associative memory under context-dependent rule reversals. Using Neuropixels probes, we recorded from LEC of 2 young and 2 aged memory-unimpaired (AU) male Long-Evans rats on an odor-place-context association task in two boxes of distinct contextual cues. Each box consists of one odor port and two choice/reward ports on the opposing wall. Two odors each correspond to reward at one choice port, and the odor-place correspondences are reversed across boxes. The number of days to reach criterion performance (>80% correct in both contexts) was similar across young and AU rats. 54% (273/505) of neurons exhibited consistent activity changes during task performance, including cue sampling, running to choice ports, and reward consumption (initial learning: sampling=30%, running=38%, reward=30% out of 124 neurons; criterion performance: sampling=28%, running=56%, reward=15% out of 149 neurons). With learning, activity of an increased proportion of task-relevant neurons became modulated by context (initial learning: 27%; criterion performance: 50%). The period of maximal differential firing for odor 1 vs. odor 2 trials (from latter half of cue sampling to choice port nosepoke) was accompanied by increased power of 20-40 Hz oscillations. When successful retrieval of odor-place-context associations is necessary for reward, LEC recruits more neurons during delay (between cue sampling and choice port nosepoke) and exhibits more context-modulated activity along with prolonged 20-40 Hz oscillations. Young and AU rats demonstrated similarities in the behavioral expression and neural correlates of associative memory, laying the groundwork to investigate LEC information processing deficits among aged memory-impaired (AI) rats.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

Location: MCP Hall A

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National Institute of Neurological Disorders and Stroke of the U.S. Public Health Service (R01 NS039456)
STI2030-Major Projects (2022ZD0205500)
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Title: Impaired spatial coding of the hippocampus in a dentate gyrus hypoplasia mouse model

Authors: *X. CHEN[1,2], A. RATTNER[3], N. CHENG[4], C. WANG[4,2], J. J. KNIERIM[5]; [1]Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Zanvyl Krieger Mind/Brain Institute, Johns Hopkins University, Baltimore, MD; [3]Johns Hopkins Univ., Baltimore, MD; [4]Shenzhen Inst. of Advanced Technol., Chinese Acad. of Sci., Shenzhen, China; [5]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: (**Objective and Rationale**) The dentate gyrus (DG) of the hippocampus is thought to orthogonalize inputs from the entorhinal cortex and relay the pattern-separated information to the CA3 region. In this study, we investigated the contribution of the DG to spatial coding properties of CA1 neurons in a mouse model of congenital hypoplasia of the DG. In this model, a deficiency in the *Wntless* (Wls) gene, specifically in cells with *Gfap-Cre*, led to an almost total absence of granule cells in the hippocampus. (**Methods**) We conducted *in vivo* calcium imaging from CA1 principal cells in ten mutant mice (five males, five females) and ten wild-type littermates (six males, four females). Mice were engaged in two tasks: shuttling along a 152.4 cm linear track and freely foraging in a 60 × 60 cm^2 box. (**Results**) We found that the calcium event rate of CA1 cells was similar for both sexes and genotypes. The spatial selectivity of CA1 cells was preserved in mice without the DG. However, in the linear track task, place fields in mutant mice were more likely to be located near track terminals. The direction selectivity of CA1 cells on the linear track was similar in both genotypes. However, CA1 neurons exhibited pronounced distance selective firing from the start point in each running direction, unlike their wild-type counterparts. In the open box task, CA1 cells in mutant mice exhibited reduced place cell percentage (718 out of 1826 cells (39.3%) in mutants vs. 809 out of 1514 cells (53.4%) in wild-types) and diminished spatial information. We found no sex differences within the same genotype for all the above phenomena. Finally, the place field stability in the same environment was reduced in mutant mice compared to wild-type mice across days and sessions. This instability led to spatial correlations between different environments, and the same environments were more similar in mutant mice than in wild-type mice. (**Conclusions**) These results suggest that DG is essential for precise and reliable spatial representation, as well as contextual differentiation in CA1 neurons.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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NIH/NINDS Grant T32NS091018

Title: Potentiation of hippocampal place fields in rats occurs in an episodic manner related to distal landmark changes

Authors: *P. OZEL[1,2], G. RAO[2], V. M. MULLER[2], V. PULIYADI[3], J. J. KNIERIM[2,4,3,1]; [1]Johns Hopkins Sch. of Med., Baltimore, MD; [2]Zanvyl Krieger Mind/Brain Inst., [3]The Dept. of Psychological & Brain Sci., [4]Kavli Neurosci. Discovery Inst. (NDI), Johns Hopkins Univ., Baltimore, MD

Abstract: Hippocampal place cells are modulated, or even form new place fields, by objects and events at the cells' preferred firing locations. This coding scheme may reflect the representation of nonspatial information within a spatial framework, providing a method for hippocampal representations to integrate behaviorally relevant aspects needed for episodic memory. O'Keefe (1976) first described a phenomenon where hippocampal cells began to fire as an object or food source was removed or added, termed "misplace units." Previous work demonstrates that CA1 and CA3 neurons develop new fields at the location of object manipulation (Manns & Eichenbaum, 2009; Deshmukh & Knierim, 2013). However, it remains to be studied if and how cells that form new place fields (or increase their firing in a weak field) discriminate distal cue manipulation events in an episodic manner. We hypothesized that place fields would potentiate rapidly in response to salient environmental changes—specifically, distal cue removal and reinstatement—and remain active for the remainder of the session after the event.
Using Neuropixels 2.0 probes, we recorded hippocampal CA1 and CA3 neurons in Long-Evans rats (2 males, 2 females) navigating clockwise on a circular track for rewards (2-3 per lap). During each session, one of the distal cues in the environment was first removed and later reinstated. To make the cue manipulation unpredictable to the animal, the manipulation time and location varied across sessions. Of 311 place cells recorded, 41 (13%) had fields that potentiated their firing rates at some moment during the ~25-lap session. Of these 41 cells, 10 fields potentiated immediately after one of the cue manipulation events (5/41 to cue removal; 5/41 to cue reinstatement). Other fields had reversible firing dependent on the presence or absence of the cue (4/41 potentiated fields). The results of this study suggest that a subpopulation of place fields potentiate in an episodic manner to salient events in the environment and discriminate between event type (cue removal and reinstatement). We propose that hippocampal place cells can flexibly encode environmentally relevant experience through place field potentiation of the spatial cognitive map.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Dr. Miriam and Sheldon G. Adelson Medical Research

Title: Age-related alterations in neural activity of granule cells and mossy cells in the dentate gyrus of mice

Authors: *S. KIM[1], X. YU[1], D. GOODSMITH[1,8,9], J. SMITH[2], H. KIM[1], J. J. KNIERIM[8,10,11], K. M. CHRISTIAN[1], G.-L. MING[1,3,4,5], H. SONG[1,3,4,6,7];
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Abstract: Spatially modulated firing in the form of place fields within the hippocampus establishes a foundation for a cognitive map to support the formation of episodic memory. Among the hippocampal subregions, the dentate gyrus (DG) uniquely houses two types of excitatory cells: granule cells (GCs) and mossy cells (MCs), which exhibit distinct rates of activation. Most studies of the in vivo spatial firing characteristics that distinguish these different cell types during exploratory behavior come from animals < 6 months of age, and limited knowledge exists regarding these characteristics in older animals. In this study, we recorded putative excitatory cells from the dentate gyrus of the hippocampus as they navigated familiar environments. We used machine learning techniques to distinguish between GCs and MCs and compared the spatial firing patterns of these cells in the DG of mice aged over 24 weeks (just before or around the time that mice begin to show potential cognitive deficits in navigation; Brito et al. 2023) with those of mice aged between 12 and 24 weeks. The findings reveal that GCs in the younger animals are more likely to demonstrate place fields within a given environment

compared to GCs in the older animals. MCs in the older animals exhibit higher mean firing rates than those in younger animals. While general properties of individual place fields, such as number and size of place fields, remain similar between the younger and older animals for both GCs and MCs, MCs exhibit less remapping in the older animals compared to the younger animals. Collectively, our electrophysiological recordings of single DG cells in freely behaving mice suggest that GCs and MCs in the DG of older animals exhibit age-related changes in some spatial firing properties. Furthermore, these findings provide insight into how the firing patterns of DG cells and their response to contextual changes are influenced by age in vivo.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Title: Change of hippocampal theta frequency predicts the extent of recalibration of path integration

Authors: *S.-B. PARK[1], M. S. MADHAV[3,1,4], R. P. JAYAKUMAR[2], N. J. COWAN[5,7], J. J. KNIERIM[1,6,4];
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Abstract: Path integration (PI) refers to the ability to estimate one's current location based on the direction and distance traveled from a previously visited location. Such a computation requires a gain factor that relates the magnitude of distance traveled in the world to the magnitude of change in the neural representation of position. Models based on place cells and grid cells have treated this PI gain as a constant that equals 1. However, a study using VR in moving rats (Jayakumar, Madhav et al., 2019) demonstrated that PI gain recalibrates to new values when a conflict is introduced between the distance traveled in a fixed frame of reference (i.e., the world) and the distance traveled relative to an array of moving visual landmarks. The extent of this recalibration varied for each session, and the factors influencing this recalibration remain

unknown. Theta activity in the hippocampus is crucial for place representation in rodents (Buzsaki, 2005). Therefore, we investigated whether theta activity would predict the amount of gain recalibration.We analyzed single unit and LFP data from the CA1 region of 4 male, Long-Evans rats previously reported by Jayakumar, Madhav et al. (2019). Visual landmarks were projected onto the interior surface of a 7-ft diam. hemispherical dome surrounding a circular track. As the rat moved CCW around the track for food reward, the landmarks were rotated by an experimental gain factor based on the rat's speed, providing the rat with the illusion that it was moving faster or slower than it really was. After ~30 laps at a specific gain, the landmarks were turned off, and the rat had to rely on PI alone to update its hippocampal cognitive map. PI gain was measured as the rate of updating of position on the hippocampal map divided by the actual rate of change of position of the rat around the track. We measured the difference of theta frequency between the time when landmarks were extinguished and the start of the experiment. There was a significant correlation between this theta frequency change and the extent of recalibration of PI after the landmarks were turned off ($r = 0.45$, $p = 0.012$). The change in theta frequency, measured when the conflict was ongoing was typically greatest when the conflict between landmarks and PI was increasing, and the frequency appeared to trend back toward its starting value when the experimental gain was held constant, presumably when the PI gain was undergoing recalibration. We hypothesize that change in theta frequency correlates with the moment-by-moment conflict between PI and the external landmarks, which is gradually resolved as PI recalibration progresses.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Program #/Poster #: PSTR140.14/O1

Topic: H.09. Spatial Navigation

Support: NIH RF1 NS132041-01
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Title: Hippocampus-neocortex interactions at theta timescale

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Abstract: Theta oscillations (5-10 Hz) provide temporal windows for coordinating neural activity within large-scale networks. Bidirectional communication between hippocampus (HC) and neocortex (NC) is crucial for learning and memory consolidation. In mice navigating head-fixed virtual reality (VR), both HC and NC display spatially modulated cells over behavioral timescales. Hippocampal place cells are strongly modulated by theta oscillations and display sequences at theta timescale (~125 ms). However, the interaction between HC and NC at theta timescales remains understudied. In mice (n=11), we conducted simultaneous single-unit and local field potential recordings, during VR navigation with high-density silicon probes, from CA1 (dorsal and ventral) and dentate gyrus (DG) as well as the following cortical regions: agranular retrosplenial (RSCag), parietal (PPC), primary visual (V1), and lateral visual (V2L). Within the cortex, we found that a larger fraction of fast-spiking interneurons (15-25% in PPC, V1, V2L; 80% in RSCag) were significantly phase-locked to dorsal and ventral CA1 theta compared to pyramidal cells (5-10% in PPC, V1, V2L; 30% in RSCag). RSCag interneurons had the strongest theta modulation (relative to other cortical regions) with superficial RSCag interneurons exhibiting stronger modulation than deep (mean vector length, L2/3: 0.126 vs. L5/6: 0.085). We also observed a consistent sequence of activation across brain regions with cortical interneurons firing 120-160 degrees (PPC -> V2L/V1 -> RSCag) after dorsal CA1 pyramidal cell population preferred theta phase. Taken together, these results suggest that feedforward inhibition from the HC may shape the temporal activity of cortical pyramidal cells to support HC 'index' consistent firing patterns, particularly in superficial cortical layers.

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Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Program #/Poster #: PSTR140.15/O2

Topic: H.09. Spatial Navigation

Support: FG20621

Title: Differential Organization of Monosynaptic Inputs to GABAergic Neuron Subtypes in the Dorsal Subiculum

Authors: *P. GAO[1], Q. YE[2], M. RIVERA[3], X. XU[4];
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Abstract: Differential Organization of Monosynaptic Inputs to GABAergic Neuron Subtypes in the Dorsal SubiculumPan Gao[1,2], Valeria Quezada, Matthew Rivera, Layla Ajouz, Aayush Raman, Xiangmin Xu[1,2]Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine, Irvine, CA 92697-1275, USAThe Center for Neural Circuit

Mapping, University of California, Irvine, Irvine, CA 92697, USAThe hippocampal formation, comprising the dentate gyrus (DG), hippocampus proper, and subiculum (SUB), is pivotal in episodic memory and spatial navigation. Although the SUB is traditionally viewed as a relay station between CA1 and downstream regions, recent evidence data suggests supports that it SUB has distinct circuit organizational and functional characteristics. This study aims to explore these distinctions by examiningexamine the neural circuitry connections of excitatory and inhibitory cells in the distal part of the dorsal subiculum (dSUB). Utilizing an our established monosynaptic rabies virus tracing system, we targeted mapped local and long-range circuit connections to glutamatergic and GABAergic cells, including three major subtypes of GABAergic cells: parvalbumin (PV), somatostatin (SOM), and vasoactive intestinal peptide-expressing (VIP) in the dSUB. Our findings indicate that inputs to Gad2+ and Camk2a+ cells are comparable in terms of regional input regions patterns and strengths, primarily originating from CA1, subiculum, postsubiculum, medial septal diagonal band, thalamus, and entorhinal cortex. However, differences in input strengths were observed among the GABAergic subtypes. Compared with VIP+ cells, ; SOM+ and PV+ cells received significantly more inputs from the thalamus (% inputs, SOM: 0.869± 0.124, PV:1.803± 0.284, VIP: 0.205± 0.1. CSI, SOM :2.083 ± 0.265, PV: 2.036± 0.284, VIP: 0.210± 0.093.) and postsubiculum (% inputs, SOM: 0.1.379± 0.363, PV:2.694± 0.862, VIP: 0.315± 0.295. CSI, SOM :2.950± 0.911, PV: 2.525± 0.695, VIP: 0.278± 0.242). [Can you please add your quantitative CSI values here]. All these cell types were found to receive putative GABAergic long-range inputs from the CA1 oriens layers. These novel new circuit mapping results enhance provide us with a new our understanding of the operational neural circuit basis of specific SUB neuroncell types in within the SUB, contributing to a deeper insight into its role within the hippocampal formation networks.

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Poster

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Title: Latrophilin-2 regulates topographic spatial information processing in the hippocampus

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[1]Neurobio., Stanford Univ., Stanford, CA; [2]Biol., Stanford Univ., Stanford, CA; [3]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: The hippocampus plays a critical role in spatial learning and navigation. The neural circuitry of the hippocampal formation is topographically organized, such that the medial entorhinal cortex (mEC) projects to the proximal CA1 and then innervates the distal subiculum (medial network); while the lateral entorhinal cortex projects to the distal CA1 and then innervates the proximal subiculum (lateral network). Correspondingly, neurons in the medial network are more spatially tuned, with enriched functional cell types such as grid cells and place cells. Previous studies have found that teneurin-3 (Ten3) and latrophilin-2 (Lphn2) guide the topographic circuit assembly of CA1 to subiculum connections in both networks (Berns et al., 2018, Pederick et al., 2021). However, it remains unknown whether this molecular guidance to the circuit topography underlies the functional spatial mapping along the CA1 to subiculum axis. Here, we used miniscope calcium imaging to record neurons along the proximodistal axis of the subiculum while the animal was freely behaving in 2D environments. In Nts-Cre; Lphn2fl/fl mice (Lphn2 cKO, n = 11), in which Lphn2 was conditionally knocked out in the subiculum, we found that the overall calcium event rate for all subicular neurons was decreased compared to the control mice (n = 10 mice). For spatial and head direction coding in the subiculum, the tuning properties of place cells and head direction cells were largely preserved (i.e., spatial information, field size, stability, mean vector length), except for the decreased peak calcium event rate for both cell types. However, along the proximodistal axis of the subiculum, the anatomical distribution of place cells in the Lphn2 cKO mice significantly shifted towards the proximal side compared to the control. In comparison, subicular head direction cells did not change their anatomical locations, suggesting that head direction coding is largely independent of this CA1 to subiculum circuit alteration. Together, our results revealed a molecular mechanism regulating the topographic spatial information processing in the hippocampal circuits.

Disclosures: Y. Sun: None. **D. Pederick:** None. **X. Xu:** None. **L. Luo:** None. **L.M. Giocomo:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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James S McDonnell Foundation Scholar Award
Vallee Scholar Award

Title: Non-local coding in medial entorhinal cortex independent from sharp-wave ripples

Authors: *E. A. AERY JONES[1], I. I. C. LOW[2], F. S. CHO[1], L. M. GIOCOMO[1];
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Abstract: Neurons can collectively represent the current sensory experience while an animal is engaged with its external environment or a remote sensory experience while an animal is disengaged. These remote representations support computations critical for learning, such as consolidating paths to rewards. Neurons in the medial entorhinal cortex (MEC) reflect the animal's current location during movement, but little is known about what MEC neurons collectively represent during immobility, when the animal might be disengaged from the environment. Here, we recorded neurons in superficial MEC layer and dorsal CA1 as mice learned to associate two pairs of rewarded locations. We found that during immobility, the MEC neural population frequently represented positions far from the animal's location. MEC non-local coding had only been previously reported during sharp-wave ripples (SWRs) from the downstream hippocampus, yet we observed non-local coding was far more common outside of SWRs. At rewarded locations, MEC represented relevant task information which changed in a task rule-dependent manner. Future work will characterize which cells are involved in non-local coding and how non-local coding is coordinated between MEC and CA1. We propose that MEC non-local coding could help animals learn relevant spatial information by providing a substrate to strengthen contextual associations.

Disclosures: E.A. Aery Jones: None. **I.I.C. Low:** None. **F.S. Cho:** None. **L.M. Giocomo:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Title: Rapid induction of place fields in RSC and V1 by holographic stimulation during spatial learning.

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[1]Stanford Univ., Stanford, CA; [2]Stanford Univ. CNC, Stanford Univ., Palo Alto, CA; [3]Neurobio., Stanford Univ., Stanford, CA; [4]Allentown LLC, Renton, WA; [5]Mol. Genet., Allen Inst. For Brain Sci., Seattle, WA; [6]Allen Inst. For Brain Sci., Seattle, WA, ; [7]Allen Inst. for Brain Sci., Seattle, WA, ; [8]Stanford, Stanford, CA

Abstract: Animals quickly learn to navigate in new environments by integrating sensory cues with self-motion information. The retrosplenial cortex (RSC) and the primary visual cortex (V1), a key input to RSC, play crucial roles in this process by encoding visual landmarks and self-motion. To investigate the dynamics of landmark and position encoding in RSC and V1, we combine two-photon calcium imaging with holographic optogenetic stimulation in mice navigating virtual reality (VR) environments. Specifically, we aim to determine if the spatial code of individual neurons can be influenced by repeatedly activating neurons at select positions in the VR, as mice explore both novel and familiar environments. In novel environments, spatially organized activity emerges rapidly in RSC. These representations stabilize within days, with neurons exhibiting one or multiple place fields. Repeated stimulation of RSC neurons at specific locations in the VR can induce new place fields at stimulation-paired positions, a process that occurs rapidly within a single session. Interestingly, the capacity to induce new place fields is highly dependent on the novelty of the environment. Optogenetic stimulation has little lasting influence on the activity of targeted neurons when mice explore a familiar environment, suggesting that the plasticity of spatial representations in RSC is gated by environmental novelty. Similarly, in V1, targeted optogenetic activation biases neuronal activity towards stimulation-paired locations in novel environments, but not in familiar ones. Our data demonstrate a rapid emergence of stable, spatially organized neuronal activity in RSC and V1 as animals explore novel environments. We hypothesize that during the initial formation of spatial representations, a complex interplay of factors, including input to individual neurons, intrinsic neuronal excitability, and network-level dynamics, shapes the spatial coding properties of individual cells. This initial representation undergoes rapid refinement and stabilization, resulting in a robust neural representation that is resistant to perturbations once established.

Disclosures: A. Attinger: None. **A. Drinnenberg:** None. **C. Dong:** None. **L. Siverts:** None. **T.L. Daigle:** None. **K. Deisseroth:** None. **L.M. Giocomo:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Howard Hughes Medical Institute

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U19NS132720

Title: A Multi-Region Brain Model to Shed Light on the Role of Hippocampus in Spatially Embedded Decision Tasks

Authors: *Y. XIE[1], J. HWANG[2], C. D. BRODY[1,3], D. W. TANK[1], I. R. FIETE[2];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]MIT, Cambridge, MA; [3]Howard Hughes Medical Institute, Chevy Chase, MD

Abstract: The hippocampus is critical in contextual and associative learning, while the cortex is key in evidence accumulation. A recent study, in which mice ran through a T-maze with towers on each side and had to turn to the side with more towers at the end (Nieh et al., 2021), demonstrated that CA1 forms cognitive maps that conjunctively represent both spatial position and integrated evidence. Further, a preliminary study (unpublished) found that the optogenetic inactivation of the hippocampus leads to a significant bias in hard trials. While Mochizuki-Freeman et al. (2023) and Lee et al. (2022) have built deep reinforcement learning models based on the same task, no model exists for insights concerning the interactions of hippocampus (HC), medial entorhinal cortex (MEC), and prefrontal cortex (PFC) in spatially embedded decision tasks. Here, we developed a multi-region brain model with a structured entorhinal-hippocampal circuit adapted from Chandra et al. (2023), concatenated with an action-selection recurrent neural network (RNN). The modularity of our model allows for testing the counterfactual of various inputs into grid cell computations for insights on place cell representations and agent learning behaviors in the described task, allowing dissection of why such hippocampal cognitive maps may arise. With multiple model variants tested under a reinforcement learning setup, we found jointly tuning position and evidence in grid cell modules promotes rapid learning, as opposed to i.e. grid cells disjointly tune task variables in separate modules, or tune only one task variable. Notably, the representation of place cells within this model, which arises solely from the hippocampal interaction with MEC, qualitatively mirrors the experimental observations reported by Nieh et al. (2021). Specifically, place cells in our model also formed firing fields in evidence space that spanned small segments of evidence values, and a small fraction of place cells are choice-specific. Our finding predicts that grid cells are co-tuned to position and evidence. Together, our computational framework offers a systematic approach to analyzing the roles of multiple regions involved in a spatially embedded decision-making process and suggesting new experimental investigations.

Disclosures: Y. Xie: None. **J. Hwang:** None. **C.D. Brody:** None. **D.W. Tank:** None. **I.R. Fiete:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Title: The infralimbic cortex contributes to working memory by representing the structure of the task phase, while the prelimbic only represents cue and choice representation.

Authors: *H. HA, E.-H. PARK, I. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Literature suggests that both the hippocampus (HP) and the medial prefrontal cortex (mPFC) play key roles in working memory (WM), but their functional relationships remain unclear. In the mPFC, the infralimbic cortex (IL) receives more projections from the intermediate HP (iHP) than the prelimbic cortex (PL). In this study, we aimed to dissociate the neural correlates of IL and PL in relation to the iHP in WM. In our WM task, body-fixed rats (male Long-Evans, n=5) ran on a cylindrical treadmill to navigate in a VR environment (i.e., VR context). Once a trial starts, in the sample phase, the rat experienced one of 4 VR contexts. Then, the rat ran in a gray tunnel for 3s for the delay phase. Finally, in the test phase, two water ports protruded to deliver honey water when a correct port was licked (120 trials/session). A hyperdrive was implanted targeting the PL and IL simultaneously for recording single units with 24 tetrodes. In the same rat, cannulas were implanted bilaterally to inject muscimol (MUS, 0.3-0.5 μL/site) into the iHP when needed. Injecting MUS in the HP resulted in a decrease in WM performance relative to vehicle conditions (mean accuracy drop from 86% to 62%, $p<0.001$). Our preliminary results show that the neural firing in the mPFC was significantly modulated by the VR environment and choice response. Specifically, the spiking activities of the cells in the PL (n=49) and IL (n=39) were modulated similarly by the VR context and choice response in the sample and delay phases. Inactivating the iHP disrupted the contextual modulation of neural firing in the sample phase in the PL ($p<0.01$). In the IL, the modulation of the neural firing patterns by the VR context ($p<0.05$) and choice response ($p<0.01$) decreased during the sample phase, with a significant reduction in the choice-based neural modulation in the delay phase ($p<0.001$). Some cells in the IL (9.5 %), but not the PL, that showed significant neural modulations by task-related variables represented the choice response both in the sample and delay phases, but this cell type was not found in the PL. In contrast, some neurons in the PL (13.3%) represented the VR context in the sample phase and the choice response in the delay phase, but these cells were not found in the IL. MUS injections in the iHP eliminated the activities of these functionally diverse neuronal classes recording in the WM task. Moreover, MUS injections in the iHP lowered the power of theta rhythm in the IL, but not the PL($p<0.05$). Interestingly, spiking phase relationships with theta changed significantly in the PL, but not the IL($p<0.001$). These subregional differences in neural firing in the mPFC suggest differential roles of the PL and IL in hippocampal-dependent WM.

Disclosures: H. ha: None. **E. Park:** None. **I. Lee:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Topic: H.09. Spatial Navigation

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0205000)
National Natural Science Foundation of China (32371076)

Title: The Primate Retrosplenial Cortex Translates between Hippocampal World-centered and Parietal Self-centered Representations

Authors: *Y. HUANG, A. LIU, X. XU, K. DU, D. MAO;
Inst. of Neuroscience, CEBSIT, Chinese Acad. of Sci., Shanghai, China

Abstract: We constantly align self-centered sensory inputs (egocentric) with world-centered spatial map (allocentric) to locate and orient ourselves while navigating. The hippocampus (HPC), retrosplenial cortex (RSC), and posterior parietal cortex (PPC) are key regions implicated in processing spatial information from different reference frames. However, it is unclear what exact roles these regions play particularly in primate navigation. In the present study, we trained three macaque monkeys to freely navigate in an open arena for randomly scattered food pellets while tracking their head and eye. We wirelessly recorded single neurons and local field potentials (LFPs) across HPC, RSC, and PPC. We recorded 1018 well-isolated single units (HPC, 643 neurons; RSC, 214 neurons; PPC, 161 neurons). The PPC-RSC-HPC pathway showed opposing gradients for egocentric and allocentric spatial coding, with PPC preferring the former and HPC preferring the latter, respectively. RSC carried the strongest mixed egocentric and allocentric coding, containing the largest fraction of neurons tuned to head or gaze direction, which may function as gain modulation between the two reference frames. RSC neurons also showed increased activity upon head or eye movement. Moreover, RSC exhibited preferred phase-locking to distinct frequency bands of HPC and PPC LFPs: more neurons were locked to HPC theta while this was true for PPC beta. These findings suggest that the monkey PPC-RSC-HPC pathway gradually translates between egocentric and allocentric spatial representations, with information from both reference frames converging in RSC, likely mediated by directional tuning.
Keywords: Hippocampus; retrosplenial cortex; parietal cortex; freely-moving macaques; spatial navigation; reference frame transformation; spatial representation

Disclosures: Y. Huang: None. **A. Liu:** None. **X. Xu:** None. **K. Du:** None. **D. Mao:** None.

Poster

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Topic: H.09. Spatial Navigation

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0205000)
National Natural Science Foundation of China (32371076)

Title: Disrupted spatial selectivity in the primate hippocampal-orbitofrontal circuit during navigation in virtual reality

Authors: *W. YAN[1,2], D. MAO[1,2];
[1]Ctr. for Excellence in Brain Sci. and Intelligence Technol. (Institute of Neuroscience), Shanghai, China; [2]Chinese Academy of Sciences, Beijing, China

Abstract: Abstract: Virtual reality (VR) simulating real-world (RW) situations has been increasingly used to facilitate studies of spatial navigation in primates. Successful navigation relies on the integration of many sensory inputs. It is therefore a critical but still untested question how findings from VR are implicated in RW, particularly considering the conflict between visual and vestibular inputs in VR. The hippocampus (HPC) and orbitofrontal cortex (OFC) are two key regions involved in spatial cognitive mapping. The goal of the present study is to compare HPC-OFC neural activity responses between VR versus RW during free foraging and spatial memory tasks. We trained two macaque monkeys to navigate in visually similar environments between VR and RW. We used two tasks: a free foraging task and a spatial memory task. We recorded the identical neurons across experiments using chronically implanted tetrode arrays with concurrent eye and motion tracking. Preliminary analyses revealed that spatial selectivity to various components, including position, spatial view, and head direction, was largely impaired in VR in both the right HPC and OFC. Spatial memory task elicited stronger spatial selectivity compared to that during free foraging in the same environment. Furthermore, we observed a high degree of spatial selectivity dynamics: some neurons gained, some lost, while others changed their spatial tunings to different variables from VR to RW, and across tasks. Overall, the present study interrogated how neural dynamics of spatial navigation under VR differ from that in more naturalistic conditions. Both the HPC and OFC exhibited markedly stronger spatial representations in RW compared to VR settings, and spatial selectivity was task-dependent. Although virtual navigation shares many features in common with natural navigation, we cannot equate the two in terms of the underlying neural substrates. The mismatch between visual cues and other self-motion signals has a profound effect on spatial representations. To faithfully extrapolate findings from VR to RW, more development and validation may be required.
Keywords: spatial navigation, virtual reality, real-world, hippocampus, orbitofrontal cortex, non-human primate

Disclosures: W. Yan: None. **D. Mao:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Hong Kong RGC Theme-based Research Scheme (T13-605/18-W; J.I.)

Title: Dissection of the corticohippocampal circuit underlying neuronal ensemble dynamics in spatial learning and memory

Authors: *H. XU, Z. ZHANG, P. IP;
The Sch. of Biomed. Sci., The Chinese Univ. of Hong Kong, Hong Kong, China

Abstract: Memories have been suggested to be stored in groups of neurons known as neuronal ensembles, or “engrams”, and neuroplasticity is believed to be the underlying mechanism that allows the formation or remodeling of these ensembles, thus allowing memory modifications. In the context of fear memory, the representation of the hippocampal neuronal ensemble has been characterized, while little is known about the neuronal ensemble within the hippocampus and the upstream circuits in spatial learning and memory. With recent development of whole brain imaging, it is now possible for the identification of previously unidentified, or understudied, circuitry by monosynaptic tracing. In this study, we will first establish a spatial learning task that requires coordinated activities of dorsal (d)CA1 neurons. We will then examine the functional importance of dCA1 subregion in this learning task using chemogenetics, and calcium recording. Our working hypothesis is that CA1, as a major output region of the hippocampus, integrates inputs from multiple brain regions to generate task-relevant outputs to downstream region in spatial learning and memory. The study will characterize novel and understudied upstream inputs to a subregion of the CA1, and will provide a deeper understanding in the functional importance of this corticohippocampal circuit in spatial learning and memory.

Disclosures: H. Xu: None. **Z. Zhang:** None. **P. Ip:** None.

Poster

PSTR140: Cortico-Hippocampal Interactions Underlying Spatial Navigation I

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Topic: H.09. Spatial Navigation

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Title: Cortical pathways for modulating hippocampal place cell ensemble dynamics

Authors: *Z. ZHANG, H. XU, V. C.-K. CHEUNG, P. IP;
Sch. of Biomed. Sci., The Chinese Univ. of Hong Kong, Hong Kong, China

Abstract: The classical hippocampal-entorhinal circuit is well-documented for its role in spatial navigation and memory, yet the contributions of adjacent, understudied cortical regions to hippocampal place cell dynamics remain underexplored. Using monosynaptic tracing, our lab has identified and validated several understudied cortical regions providing direct inputs to the CA1 region of the hippocampus. This current study proposes to investigate how specific understudied cortices may modulate hippocampal place cell ensemble dynamics, potentially augmenting the traditional entorhinal-hippocampal pathway in processing spatial and contextual information. Using mouse model, this study utilizes in vivo one-photon calcium imaging recordings paired with chemo-genetic manipulation techniques to delineate the cortical pathways on hippocampal neural circuits. Our preliminary data reveal that the behavioral performance of mice in the inhibition group was severely disrupted during the delay-nonmatching-to-place T-maze task. Additionally, the targeted inhibitions influenced the remapping and stability of the hippocampal place cell maps in the CA1 region. Our ongoing work will incorporate computational modeling to simulate the interactions between cortical regions and the entorhinal-hippocampal circuit. These models will allow us to predict the impact of cortical modulation on the encoding and retrieval functions of hippocampal place cells, enriching our understanding of the broader neural network involved in memory and spatial processing. The anticipated results will not only clarify the role of cortical pathways in modulating hippocampal dynamics but also potentially identify new targets for enhancing cognitive functions and treating memory impairments. By broadening the scope beyond traditional pathways, this study seeks to advance our comprehension of cortical contributions to hippocampal spatial mapping and memory encoding.

Disclosures: Z. Zhang: None. **H. Xu:** None. **V.C. Cheung:** None. **P. Ip:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Program #/Poster #: PSTR141.01/O12

Topic: H.11. Language

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Title: Neural Correlates of Overt, Mimed, and Imagined Speech Production Types in Electrocorticography

Authors: *J. KWON[1], G. LEE[1], C. CHUNG[2];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Neurosurg., Seoul Natl. Univesity, Seoul, Korea, Republic of

Abstract: Previous research in speech production decoding has predominantly focused on overt speech, utilizing the audible outputs of participants as a benchmark to evaluate decoder performance. However, since the primary beneficiaries of speech decoders are often those unable to produce audible speech, developing decoders for imagined speech is essential. Despite the significance of this advancement, decoding imagined speech faces substantial challenges due to the absence of a verifiable ground truth, making direct comparison infeasible. Moreover, although differences between overt and imagined speech are recognized, the specifics regarding whether these differences are spatial, temporal, or a combination of both remain unclear. Mimed speech, hypothesized as an intermediary form between overt and imagined speech, with its proximity to either form still undetermined.
To address these issues, our study employed high-resolution electrocorticography (ECoG) to simultaneously investigate the neural correlates and decoder performance across all three speech production types—*overt*, *mimed*, and *imagined* during the time before the onset of audible speech in *overt* or the compatible time in *mimed* and *imagined*. During the interval from word presentation to before speech onset, we found that *overt* and *mimed* speech exhibited the highest similarity in neural activity within the sensorimotor cortex, particularly in the high gamma frequency band. Additionally, *mimed* and *imagined* speech showed a secondary level of similarity in the superior temporal gyrus. These findings underscore the distinct yet overlapping neural activation patterns associated with different speech production types, emphasizing the importance of high gamma signals in understanding these relationships.
Our results provide the strong evidence that mimed speech bridges the gap between overt and imagined speech, particularly in decoding pre-audible neural signals. This approach enabled a detailed examination of the spatial and temporal contributions unique to each type, shedding light on their neural distinctions and providing insights into more effective language Brain-Computer Interfaces for speech-impaired individuals.

Disclosures: J. Kwon: None. **G. Lee:** None. **C. Chung:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Topic: H.11. Language

Support: Alchemist Project (20012355, Fully implantable closed loop Brain to X for voice communication) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

Title: Difference in Speech Spectrogram Synthesis in Overt, Mimed, amd Imagined Speech: human electrocorticography study

Authors: *C. CHUNG[1], J. KWON[2], Y. PARK[3], G. LEE[3];
[1]Seoul Natl. Univesity, Seoul, Korea, Republic of; [2]Brain&Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Speech decoding has been focused on overt speech production. Previously, we implemented Linear Discriminant Analysis to synthesize speech spectrograms from high gamma activity (HGA) during over speech production with high accuracy (Meng, Kevin et al., 2023). The model features were clustered in the postcentral and superior temporal gyrus. Meanwhile, when this model was tested in mimed and imagined speech, performance metrics showed only moderate success in mimed speech with a chance-level accuracy in imagined speech, highlighting a significant drop in model performance when no speech articulation.
However, for use in speech impaired individuals, imagined speech decoding is definitely warranted. This study aimed to bridges this gap by elucidating the difference in neural mechanisms of *overt, mimed, and imagined speech* using high-resolution electrocorticography (ECoG) data for 3 epilepsy patients.
Since the language network could be divided into 2 distinct systems of perceptual and motor one (Fedorenko, Evelina et al., 2024), we hypothesize that the postcentral gyrus and superior temporal gyrus are primarily engaged during overt and mimed speech, reflecting the involvement of motor system associated with speech articulation. In contrast, for imagined speech, regions associated with perceptual system play a more critical role. Furthermore, neural recruitment patterns in imagined and mimed speech might be more similar, attributable to the inhibition of speech sound production and more aligned with the perceptual system.
Here, we calculated the Dynamic Time Warping (DTW) correlation between speech envelopes and neural activities across various cortical regions. HGA showed the strongest DTW correlation with speech envelopes during overt and mimed speech, particularly in the postcentral, and superior and middle temporal gyrus compared to other cortical regions, with z scores above 2. In contrast, the supramarginal gyrus exhibited high DTW correlation across all three speech modes, with HGA aligning more closely between imagined and mimed speech ($r = 0.30$, Pearson's correlation) than overt speech ($r = 0.26$, Pearson's correlation).
Our results suggest that while speech motor control areas are crucial for overt and mimed speech, supramarginal areas might play a pivotal role in non-overt modalities. Therefore, for decoding imagined speech, the supramarginal area is where to develop the model, particularly with mimed speech, since still it provides the ground truth.

References

Meng, Kevin et al., J Neural Eng, 2023, doi:10.1088/1741-2552/ace7f6
Fedorenko, Evelina et al., Nature reviews, 2024, doi:10.1038/s41583-024-00802-4

Disclosures: C. Chung: None. **J. Kwon:** None. **Y. Park:** None. **G. Lee:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Title: Decoding Number of Syllables for Imagined Speech

Authors: *G. LEE[1], C. CHUNG[2];
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Abstract: INTRODUCTION Speech decoding has been a key area of focus in the human brain-computer interface (BCI) field over the past decade. While successful decoding has been reported for attempted tasks with movement, such as overt and mimed speech, producing clear sounds from imagined speech remains to be a challenge. To tackle this issue, we utilized the number of syllables as an inherent linguistic feature to predict the words imagined by the patient. In this study, we explored how the number of syllables in imagined speech can be encoded and subsequently decoded, drawing on our experimental findings. **METHODS** We recruited six patients with drug-resistant epilepsy who underwent intracranial electroencephalography (iEEG) for clinical purpose. In a single session, each of 108 words with random order was shown to the patients for three seconds after a one-second fixation slide. The words were grouped into four syllable-based categories (1, 2, 3, >4 syllables). At any moment, patients were instructed to mentally speak each word. A deep learning model, which included one bidirectional gated recurrent unit (GRU) layer and a fully-connected layer, was employed to determine the number of syllables of each word. For the model inputs, frequency bands from the iEEG signals (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-13 Hz, beta: 13-30 Hz, low gamma: 30-70 Hz, high gamma: 70-170 Hz) were used sequentially. The model's input was bootstrapped 20 times to create an accuracy distribution, and we assessed the significance of these accuracies using surrogate data. **RESULTS** The features were deemed significant for accuracy greater than 32.19% ($p<0.001$). The alpha wave envelope displayed the most significant features. These features were present across various regions, including the posterior superior temporal gyrus (pSTG), ventral sensorimotor cortex (vSMC), posterior middle temporal gyrus (pMTG), medial occipital gyrus, and angular gyrus. Utilizing these features, the decoding accuracy for the number of syllables surpassed 40% across the four designated classes. **CONCLUSIONS** In this study, we successfully demonstrated that the number of imagined syllables can be decoded from iEEG signals. The importance of the alpha envelope in vSMC suggests a neural mechanism underlying articulatory inhibition is crucial for imagined speech.

Disclosures: G. Lee: None. **C. Chung:** None.

Poster

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Title: Decoding the "Living or Non-Living" and "Body Parts or Non-Body Parts" Semantic Categories from Intracranial EEG Data

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Abstract: Various attempts are being made to decode speech from brain signals for patients with speech disabilities. Significant advancements have been made using invasive methods such as intracranial electroencephalography (iEEG). In semantic decoding, it is crucial to understand the entity being referred to. Categorical information, such as whether it is living or not and whether it is body-parts or not, can help more accurate decoding. We analyzed iEEG data from 9 participants. The "living (+/-)" and the "body-part(+/-)" sessions were conducted 4 times, each consisting of 18 trials. Each trial was divided into four blocks: fixation, listening, option, and answer. After a 3s fixation, a 5s listening block occurs where the participants are presented with questions like "which one is living? (or not?)" or "which one is the part of the body (or not)." During the option period, two images are shown for 2 seconds. As the answer block begins, the participants verbally respond to the question choosing one of the two images. We analyzed the data separately for each electrode, time period, and frequency. We analyzed the 5 different bands: alpha, beta, and gammas. (30-50Hz, 50-70Hz, and 70-150Hz) Maximum decoding performance (ROC_AUC) was 0.80 for the living(+/-) category (average across each subject: 0.69) and was 0.79 (average 0.68) for the body-parts(+/-). Several participants mistakenly spoke the opposite answer in a few trials. We investigated how these error trials were decoded separately. When examining the probability distribution of each trial, it was observed that decoding occurred in the direction of the incorrect response rather than the actual correct answer. This means that decoding was based on the direction the participants thought and prepared to speak as correct, regardless of the actual questions. Additionally, in Korean, the end phrases of the question is the same for both the living(+/-) and body-parts(+/-) sessions. Therefore, a decoding effect could occur independently of the meaning and it was necessary to check for the influence. By testing whether data from the opposite session could be decoded by the model trained for each session, we aimed to determine if the similarity of speech presented in these tasks influenced decoding. In most cases, decoding performance was either not significant or very low. However, in some timings for certain electrodes, decoding performance was as high as

it was with the original session's data. We were able to confirm that the categories of living(+/-) and body-parts(+/-) were successfully decoded. Additionally, we found that the influence of other non-semantic factors on the decoding of speech words was minimal in most cases.

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Poster

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Title: How Many Bytes Can You Take Out of Brain-To-Text Decoding?

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Abstract: Brain-computer interfaces have promising medical and scientific applications for aiding speech and studying the brain. In this work, we propose an information-based evaluation metric for brain-to-text decoders. Using this metric, we examine three methods to augment existing state-of-the-art continuous text decoders. We show that these methods, in concert, can improve brain decoding performance by upwards of 40% when compared to a baseline model. We demonstrate the existence of a compute/performance trade-off using these approaches, and establish Pareto-optimal recommendations for managing this trade-off. Finally, we provide an estimate for the idealized performance of an fMRI-based text decoder. We compare this idealized model to our current model, and evaluate the contributions of the main sources of error with our current approach. We conclude that a practical text-to-brain decoder is likely possible given further algorithmic improvements.

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Support: NIH Grant 1R01DC020088

Title: Generating falsifiable interpretations for cortical language selectivity using large language models

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Abstract: Representations from large language models have recently shown effective performance at predicting fMRI-measured BOLD response to a language stimulus. Despite their high predictive performance, these representations are largely opaque, as it is unclear what features of the language stimulus drive response for a given voxel. In this paper, we present BrainDrive, a method for generating and validating concise semantic descriptions of language selectivity in the brain. BrainDrive iteratively calls a large language model to generate a synthetic story that selectively evaluates different brain regions. We demonstrate that BrainDrive stories can be used to selectively drive BOLD response in individual voxels across language-responsive cortex. BrainDrive is further able to drive interactions between pairs of voxels and a checkerboard pattern on the cortical surface. Through targeted experiments, we find that BrainDrive is useful for recovering known voxelwise selectivity as well as suggesting potential new selectivity maps.

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Topic: H.11. Language

Title: Neural basis of sound-shape associations for pseudowords and real words

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Abstract: Sound symbolism refers to the non-arbitrary mapping between the sound of a word and its meaning, e.g. the pseudowords “lomo” and “teke” sound rounded and pointed, respectively. The neural basis of this phenomenon has mostly been studied using pseudowords. It remains unclear to what extent the mechanisms that mediate sound-symbolic associations for

pseudowords apply to natural language (e.g. for real words such as “ball” and “spike”). Here, using functional magnetic resonance imaging (fMRI), we studied the cortical activity patterns of participants while they classified auditorily presented real words and pseudowords as rounded or pointed. To avoid differences in neural processing stemming from differences in the acoustic content of real words and pseudowords, we used the phonemes present in 12 rounded (e.g. “balloon”) and 12 pointed (e.g., “scissors”) real words selected based on their roundedness/pointedness sound symbolism score (from the list of Sidhu et al., Psychonomic Bulletin & Review, 2021), to generate 12 rounded and 12 pointed pseudowords, respectively. The pseudowords were generated by randomly shuffling the phonemes contained in the real words, and by constraining the consonant-vowel order and syllable structure of pseudowords to match that of real words. These stimuli were recorded by a native speaker of American English. Participants classified the stimuli at >75% accuracy as rounded and pointed. During fMRI scanning, real words and pseudowords were presented in pseudorandom order, and participants judged whether each item was rounded or pointed. We employed multivariate pattern searchlight analyses to assess the capacity of different brain regions to decode whether an auditory item was rounded or pointed, separately for real words and pseudowords. For real words, significant decoding accuracy was observed in the left angular and superior temporal gyri, and the right precuneus. For pseudowords, significant decoding accuracy was observed in the left superior temporal sulcus, the right intraparietal sulcus, right superior temporal gyrus, and bilateral anterior cingulate cortex. Our results suggest that the neural mechanisms mediating sound-symbolic classification differ for real words and pseudowords. Auditory processing, visual imagery of objects represented by the words, and semantic processing appear to underlie classification of real words. However, classification of pseudowords seems to require multiple brain regions involved in phonological and multisensory processing. Our findings indicate that multiple neural processes mediate sound symbolism and that these processes differ between real words and pseudowords.

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Title: Neural representations of auditory and visual features underlying sound symbolism

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Abstract: Sound symbolism refers to a non-arbitrary correspondence between the sound of a word and its meaning. Previous research has identified underlying acoustic and visual parameters predictive of sound-symbolic mapping between auditory pseudowords, like “moh-loh” and “keh-teh”, to rounded and pointed visual shapes, respectively. However, how stimulus features are integrated in the brain to support these crossmodal correspondences remains unknown. Here, we used functional magnetic resonance imaging (fMRI) to examine the cortical activity patterns associated with perceiving auditory pseudowords and visual shapes. In separate sessions, participants (N = 24, 14 F, 22.6 +/- 3.8 years) listened to 12 auditory pseudowords or viewed 12 visual shapes that were individually presented twice per functional run. The stimuli were selected to span across the rounded and pointed dimensions based on empirical ratings. Blood oxygen level-dependent (BOLD) responses to each stimulus type were estimated using the general linear model. We constructed representational dissimilarity matrices (RDMs) of the estimated fMRI BOLD responses within regions of interest for each participant by calculating the cross-validated Mahalanobis distance between all pseudoword pairs (auditory RDM) and all visual shape pairs (visual RDM). To investigate the underlying representational structure of the activity patterns, we performed a second-order correlation between the auditory and visual RDMs to different model RDMs based on the participants’ perceptual ratings of roundedness/pointedness or acoustic features of the pseudowords (spectral tilt, the fast Fourier transform, and the speech envelope). Preliminary results show that auditory RDMs in the superior temporal gyrus significantly correlated with the RDM of the auditory perceptual ratings, whereas those in Broca’s area significantly correlated with the spectral tilt RDM. Interestingly, the visual RDMs in primary visual cortex significantly correlated with the spectral tilt RDM, suggesting processing of acoustic features relevant for crossmodal correspondences. Together, these results provide support for crossmodal processing of low- and high-level stimulus features in sensory and language regions to enable sound-symbolic mappings.

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Title: Neural basis of sound-shape associations: an analysis of shape ratings and acoustic features of pseudowords

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Abstract: Sound symbolism refers to the mapping between the sound of a word and its meaning. It is often studied in terms of crossmodal correspondences in which speech sounds are associated with non-auditory features, such as shape (e.g., the pseudowords /kɛke/ and /molo/ are judged to sound pointed and rounded, respectively). Prior work asked participants to rate, using a numeric rounded/pointed scale, each of 537 bi-syllabic pseudowords recorded by a native speaker of American English. Then, a machine-learning "K-nearest neighbors" (KNN) algorithm was used to identify the combination of acoustic parameters that best predicted the rounded/pointed ratings. The optimal combination included six acoustic features: the fast Fourier transform, the speech envelope, spectral tilt, pseudoword duration, shimmer, and the fraction of unvoiced frames. Here, we investigated the neural processes associated with these acoustic features and rounded/pointed ratings of a 12-item subset of the auditory pseudowords. The pairwise Euclidean distances between pseudowords in a six-dimensional parameter space (based on the six acoustic features indicated by the KNN algorithm) were used to create a representational dissimilarity matrix (RDM). A searchlight was used to construct RDMs from the pairwise dissimilarity of the blood oxygenation level-dependent (BOLD) signals associated with the pseudowords, in 9 mm spherical regions centered on each voxel in the cerebral cortex. We used representational similarity analysis (RSA), a multivariate analysis, to examine the correlations between these searchlight RDMs and the acoustics RDM based on the KNN model. A significant second-order correlation between the RDMs was found in the left precuneus, an area associated with visual imagery. Participants also rated the pseudowords on a rounded/pointed scale during and immediately after a functional magnetic resonance imaging (fMRI) scan. The post-scan rating task presented each pseudoword 25 times; from these data, we tabulated mean ratings for each pseudoword from each participant. These participant means were used to construct an RDM from the pairwise correlations of ratings. RSA examining the correlations of the BOLD searchlight RDMs with the ratings RDM found a significant cluster in left V4, an area associated with visual shape processing, suggesting crossmodal processing of the auditory pseudowords. Thus, these results converge, consistent with the idea that sound-symbolic shape processing of auditory pseudowords might involve visual shape imagery.

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Title: No influence of musical training on the cortical contribution to the speech-FFR and its modulation through selective attention

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Abstract: Previous research has shown that musical training can lead to differences in certain neural responses to auditory stimuli. In particular, musicians were found to exhibit stronger subcortical responses to speech sounds than non-musicians. Among these responses is the frequency-following response at the fundamental frequency of a speech signal (speech-FFR). However, the speech-FFR exhibits not only a subcortical, but also a cortical component. It remains unclear whether the cortical component of the speech-FFR may be influenced by musical experience as well. Moreover, we recently showed that the cortical component is modulated by selective attention (Schüller et al., J. Neurosci. 43:7429, 2023), but whether this attentional modulation is subject to musical training has not yet been studied.In this study, we acquired magnetoencephalography (MEG) recordings to investigate the cortical contribution to the speech-FFR in 52 participants with varying levels of musical expertise. Participants were presented with two audiobooks from different speakers, with instructions to selectively attend to one while disregarding the other. We analyzed the data by computing temporal response functions (TRFs) to examine the source-reconstructed activity in the auditory cortex, specifically focusing on two acoustic features related to the fundamental frequency of speech, which characterize the speech-FFR.Our findings revealed significant differences in attentional modulation for both acoustic features, consistent with our prior research. However, we observed no modulation of the responses based on musical training. Both musicians and non-musicians exhibited similar cortical contributions to the speech-FFR. Furthermore, the attentional modulation observed was not influenced by musical training. Our results suggest that the subcortical and cortical contribution to the speech-FFR play at least partly different roles in speech processing.

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Title: Neural Dynamics of Automatic and Prompted Speech Production

Authors: *A. KHALILIAN-GOURTANI[1], E. JENSEN[2], F. ZHOU[1], P. DUGAN[3], W. DOYLE[1], D. FRIEDMAN[1], O. DEVINSKY[1], A. FLINKER[1];
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Abstract: Introduction: Speech production tasks are employed to pinpoint language areas during surgical planning in order to prevent language deficit after resection. Neuroimaging research (fMRI and PET) demonstrate that automatic (well-practiced, overlearned) speech tasks do not consistently activate all language related sites. Electrocorticography (ECoG) studies mostly focus on prompted speech production and associate recruitment of different areas to different phases of speech production. However, the exact timing and extent of left hemisphere involvement during automatic speech and its relation to prompted speech remain unclear. Method: We use ECoG recordings from seven neurosurgical patients with electrodes sampling perisylvian cortex while they perform speech production tasks. In the prompted condition, participants repeat the words after hearing (auditory repetition) and read the words visually presented (word reading). For automatic speech, participants count numbers and recite the name of days and months. We extract neural activity (high gamma broadband: 70-150 Hz) locked to word production onset. Results: We evaluate neural activity in each task before (-0.5s - 0) and after (0 - 0.5s) articulation onset. While speech production recruits similar regions in all tasks, higher neural activity in frontal cortex is observed for the prompted condition compared to automatic during pre-articulation. To statistically evaluate this effect, we employ a linear mixed effect model with prompted condition as the fixed effect and electrode and subject as random effects. We find electrodes with significant ($p<0.001$, FDR corrected) higher activation for the prompted condition localized to pre-central, inferior and middle frontal gyri. To investigate the temporal dynamics, we employ an unsupervised clustering of temporal neural activity locked to articulation across electrodes (k-means with 5 clusters). While the clusters localized to auditory and speech motor cortices show similar mean high-gamma activity across conditions, we report a specific cluster of electrode localized to pre-central and inferior frontal gyri with mean activity peaking 250 msec before articulation onset specifically for the prompted condition, and no activity during automatic speech. Conclusion: We evaluate neural dynamics of perisylvian regions during prompted and automatic speech. We report recruitment of frontal regions before articulation specific to the prompted condition. The dynamics of this cluster suggests its role in transformation from a stimulus code to an articulatory plan. In future, we aim to investigate these dynamics using encoding and decoding frameworks.

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Poster

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Title: Event-related potentials to Turkish case and number errors in a cross-modal picture-verification task

Authors: *M. J. B. LOBEL[1], J. MOSES[2], A. K. LODHI[3], M. C. ROSE[4], S. SHARIFOVA[5], V. MODINA[2], V. L. SHAFER[6], P. J. BROOKS[7];
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Abstract: Electroencephalography (EEG) signals associated with morphological processing are understudied as compared to studies of lexical anomalies. Further, the preponderance of the existing literature has focused on Indo-European languages, limiting generalizability. This study tested fluent speakers of Turkish (N = 18; MAge = 27.9 years) on a picture-verification task with inflected nouns as auditory stimuli. Event related potentials (ERPs) were collected using a 17-channel EEG system. Participants looked at scenes of a goat oriented towards or away (case) from one or two objects (number), and judged whether Turkish inflected nouns matched or mismatched the scenes. ERPs were time locked to error onset. We used a priori mixed linear regressions (random effects: item, participant) to examine whether mean amplitudes 300-500 ms (N400) and 500-700 ms (P600) after error onset varied by error type (lexical, case, number) at posterior sites (Cz, Pz, P3, P4). On lexical trials, more negative amplitude was observed on mismatch trials (incorrect noun) than match trials (Beta = 2.50, SE = .12, t(19770.57) = 21.24, p < .001), consistent with an N400. Greater negativity at 500-700 ms was also observed, suggesting a prolonged N400. On case trials, more positive amplitude was observed on mismatch trials (incorrect case marking) than match trials (Beta = -1.55, SE = .18, t(9874.89) = -8.70, p < .001), consistent with a P600. This effect was already apparent in the 300-500 ms window, suggesting an early and prolonged P600 (Beta = -1.47, SE = .17, t(9874.25) = -8.83, p < .001). On number trials, a small but significant difference between match and mismatch trials was observed in the 500-700 ms window (Beta = 0.51, SE = .18, t(9853.62) = 2.78, p = .005). Opposite to a priori predictions, and inconsistent with a P600, mismatch trials (incorrect number marking) had more negative mean amplitude than match trials. Post hoc analysis suggested that participants responded differently to errors of commission and omission of the plural morpheme. We ran a mixed linear model with stimulus match/mismatch and inflection (singular/ plural) as predictors. Within the P600 window, trials with plural nouns had higher mean amplitudes than those with singular nouns (Beta = 3.82, SE = .18, t(9852.76) = 21.33, p < .001). This effect was considerably larger in magnitude than the effect of stimulus match (Beta = 0.51, SE = .18, t(9852.32) = 2.85, p = .004). These results extend research on neural sensitivity to morphological violations to an understudied language. Future work will need to replicate this finding in a larger sample and extend it to other languages with distinct case and number marking systems.

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Poster

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Support: National Science Foundation

Title: Language-training effects on cortical cell distributions in gorillas

Authors: *B. ERBABA[1], W. HOPKINS[2], P. PATTERSON[3], C. NUNES[3], K. KEEL[4], C. D. STIMPSON[5,6,7], J. M. ERWIN[8], P. R. HOF[9,10], J. M. ALLMAN[11], E. E. HECHT[12], D. STOUT[13], M. K. EDLER[14], M. HILLEGAS[15], P. GANGANNA[16], C. C. SHERWOOD[15];
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Abstract: For several decades, the evolution of language has been explored through experiments designed to teach elements of human language to great apes. Exposure to language during infancy may shape brain growth trajectories, yielding distinctive phenotypes that persist into adulthood in language-trained apes. We approached this question by examining the postmortem brains of two gorillas, Koko (female, 46 years old at time of death) and Michael (male, 27 years old at time of death), who were taught to communicate through American Sign Language (ASL). Koko and Michael were reported to have understood approximately 2,000 and 600 words of spoken English and used 1,000 and 500 signs, respectively. We generated series of Nissl-stained histological sections through the left frontal lobes of these 2 language-trained gorillas to compare with 13 non-language-trained gorilla individuals. We focused on the inferior frontal cortex (Brodmann's areas 44 and 45), anterior cingulate cortex (area 24), and middle frontal cortex (area 46). We used an ImageJ analysis pipeline to quantify the total cell profile densities of both neurons and glia across all layers, and area fraction of cell profiles in the images. Cell profile measurements were regressed against mounted section thickness and residuals were analyzed. The cell profile density values of the language-trained gorillas were in the upper 85th percentile

of the sample for all cortical areas, with the exception of Michael's inferior frontal gyrus, which was in the upper 70th percentile. In addition, the area fraction of cell profiles in Koko's inferior frontal cortex and middle frontal cortex were in the upper 90% of the sample. Mann-Whitney U tests (2-tailed) showed that the two language-trained gorillas had significantly higher cell profile density than the total sample of non-language-trained gorillas in anterior cingulate cortex and middle frontal cortex ($p < 0.05$ for both areas), but not in the inferior frontal cortex. These results may reflect microstructural changes in cortical organization related to cognitive functions gained with language training. Our ongoing experiments will measure the proportions of different cell types by immunostaining. This research will help to uncover the neuroplasticity effects of language acquisition in great ape brains.

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Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Army xTech BOLT prize competition (Army Medical Research & Development Command)

Title: A brain-based reading comprehension intervention in adults: pilot results for in-scanner transcranial alternating current stimulation

Authors: *C. HONG, K. S. ABOUD;
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Abstract: One out of every five adults in the US struggles to comprehend written material. Current gold-standard reading comprehension (RC) interventions yield limited effectiveness in adults, presenting a significant public health challenge. Low literacy in adults is marked by largely in-tact but slow single-word reading processes; this low single-word automaticity cascades, leading to more effortful RC. In neuroscientific literature, "effortful RC" is supported and mitigated by key cross-network communication between the cognitive control network (CCN) and the reading and language network (RLN). In particular, previous work has found that communication between network hubs supports greater resilience to difficulty during RC. In our current pilot study, we target this "RC resilience circuit" in adult readers with a range of RC ability to determine whether we can 1.) enhance RC outcomes, and 2.) impact brain activations related to RC. To accomplish this, we administer low intensity tACS (2mA; individualized theta

frequency) to the left dorsolateral prefrontal cortex (DLPFC) and the left angular gyrus (AG) for 25 minutes while participants read expository text passages in the MRI scanner. We find early evidence that stimulation, compared to sham impacts RC measures and modulates areas important for comprehending text, including areas in the default mode network. To our knowledge, this is the first within-scanner tACS study to examine RC. This pilot study lays out a framework in which to implement non-invasive brain stimulation in the enhancement of discourse comprehension and provides insight into the effects of stimulation on brain network activation.

Disclosures: C. Hong: None. **K.S. Aboud:** None.

Poster

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Title: Familiarity or recognition: what makes readers discriminate upright letters better?

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Abstract: Fluent readers search faster for upright compared to inverted letter/akshara, but precisely how this effect develops is unclear. Either the knowledge of associating letter shapes with their corresponding sounds, or repeated viewing of letter shapes could lead to improved discrimination of upright letters. To investigate this, we conducted a battery of tests in a large group of children, ranging from pre-kindergarten to first grade. The tests included upright and inverted letter search, letter familiarity test, and a letter recognition test. As the children of this study were in the emergent literacy phase, and as face processing undergoes an inter-hemispheric displacement along with reading acquisition, we utilized the premises of this study to investigate any behavioral implication of this ongoing process and included a face processing test as well. Our main finding is that only children with high letter familiarity discriminated better between upright letters compared to inverted letters in visual search. This was true regardless of their recognition performance, a proxy for how advanced the child is within the emergent literacy phase. To investigate the unique contribution of familiarity in predicting visual search advantage for the upright letter (inverted - upright search time), we performed partial correlation analysis,

which revealed that only familiarity accuracy had a significant correlation with the upright letter search advantage, after controlling for factors such as recognition accuracy, RAN score, children's age, grade, etc. Thus, performance on letter familiarity but not letter recognition predicts the improved discrimination of upright letters during visual search. However, we did not find any conclusive results that suggest face processing changes with reading acquisition: participants were faster in search for upright compared to inverted faces, but this advantage was not correlated with letter search, letter familiarity or letter recognition accuracy. We propose that letter familiarity, letter discrimination, and letter recognition are distinct component skills of emergent literacy and may each exert different effects on the development of reading fluency.

Disclosures: J. Das: None. **S. Nag:** None. **M.N. Usha:** None. **S.P. Arun:** None.

Poster

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Title: The influence of bilingualism on gray matter volume within subregions of the hippocampal formation in the course of aging

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Abstract: With aging, the hippocampal formation (HF) shows variable structural atrophy, which is associated with a decline in memory performance. Bilingualism, however, seems to maintain

memory function with aging. The putative structural correlate to this cognitive advantage during aging is termed brain reserve. Greater bilingual engagement is related to higher gray matter volume (GMV) as a form of brain reserve in the HF. However, the differential influence of bilingualism on subregions of the HF remains unclear. Thus, we investigated inter-individual GMV differences as well as intra-individual GMV change over time in mono- and bilinguals in two HF subregions, hippocampus proper (HPr) and subicular complex (SubC), to disentangle the impact of bilingualism on the HF. We included 224 adults (19-83 years, 132 men, 97 monolinguals) from the population-based 1000BRAINS study. The sample was split into mono- and bilinguals using the Language Experience and Proficiency Questionnaire. For each subject, T1-weighted MR images were acquired via 3T Siemens Tim-TRIO scanner at two time points (t1 and t2, mean time interval 3.5 years). GMV was extracted from four regions of interest (ROIs) (left/right HPr and left/right SubC) from the Julich Brain atlas using the CAT12 toolbox (version 12.8_r1871) in SPM12. To assess (i) GMV differences in mono- vs. bilinguals, (ii) GMV changes over time, and (iii) the interaction between time point and language group, Analyses of Covariance were conducted (i) separately for t1 and t2 and (ii) over both time points (covariates: age, sex, education, intracranial volume, and, for analyses over two time points, time interval). Results were considered significant at $p < 0.05$. Cross-sectionally, we found higher GMV in bilinguals in the left SubC at t1 ($p = 0.049$), with a tendency towards this effect at t2 ($p = 0.054$). For the bilateral HPr as well as for the right SubC, there was similar GMV in mono- and bilinguals for both time points. Longitudinally, GMV decline over time was significant in the left SubC ($p = 0.002$) and the right HPr ($p = 0.044$). GMV trajectories were similar in mono- and bilinguals in all ROIs. With evidence for higher GMV in bilinguals in the left SubC, but none of the other ROIs, bilingualism appears to specifically add brain reserve to a region putatively subserving verbal memory retrieval rather than encoding (HPr) or visuo-spatial memory (right HF). Similar GMV change over time in mono- and bilinguals might reflect a persistence of brain reserve in the left SubC even when facing age-related structural decline. Altogether, the current results provide new insights into structural adaptations to bilingualism in the bilateral HF of the human brain.

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Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Topic: H.11. Language

Support: R01-DC016607
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Title: Proficiency, not age of acquisition, drives response in the language network: the case of heritage speakers.

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Abstract: What factors determine the level of cortical engagement during language processing in bilingual brains? Previous studies have implicated both proficiency—how well you know the language (e.g., Pallier et al., 2003) and age of acquisition—how young you were when you started learning the language (e.g., Wartenburger et al., 2003). However, much of the previous research on the neural basis of bilingual processing has relied on group-level fMRI analyses, which blur nearby distinct networks (e.g., Fedorenko & Blank, 2020), and on reverse inference from anatomical locations to function (e.g., Poldrack, 2011); these factors complicate the interpretation of the observed activations. Disentangling proficiency from age of acquisition also poses a general challenge given that the two tend to be correlated. Here, using an individual-subject fMRI approach, we investigate 'heritage speakers'—individuals who acquired their first language early but are no longer proficient in it. We tested 13 speakers who self-reported lower proficiency in their first (heritage) language (mean = 8.5/20) compared to their second (dominant) language (mean = 20). Participants were exposed to both the heritage and their dominant language from birth or shortly thereafter. Participants completed three 'localizer' tasks during an fMRI session that allowed us to identify their language network (Fedorenko et al., 2010), executive-function network (Duncan, 2010), and speech-perception regions (Overath et al., 2015). They then listened to short passages in their dominant language (English for all participants), as well as their heritage language (8 different languages in total). We found that the heritage and dominant languages elicited a similarly strong response in the speech-perception regions ($p=0.512$; Fig. 1). In contrast, the language network showed a stronger response to the dominant language than the heritage language ($p<0.001$). And the executive-function network showed the opposite pattern, responding more to heritage languages than the dominant language ($p<0.001$). Taken together, these results suggest that proficiency rather than age of acquisition is the main determinant of responses in the language regions. These regions respond more to languages in which the individual has greater proficiency, in line with the idea that higher proficiency enables the engagement of linguistic computations that these regions implement (e.g., Malik-Moraleda, Jouravlev et al., 2024). On the other hand, executive-function regions, which are sensitive to cognitive effort across domains, respond more to lower-proficiency languages, which are plausibly more difficult to process.

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Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Topic: H.11. Language

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Title: The interactions between semantic size, concreteness, familiarity, and arousal on RT and accuracy in a lexical decision task

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Abstract: In the past several decades, much work has examined semantic factors that contribute to the processing of words. Some semantic factors, such as concreteness, familiarity, and arousal, are well-established as affecting lexical recognition. One lexical dimension that has only recently been identified is semantic size (the magnitude associated with the meaning of a word). Our current investigation examines the interactions between semantic size and these previously established dimensions (concreteness, familiarity, arousal) in response time (RT; in milliseconds) and accuracy at the trial level in a lexical decision task (n= 144 native English speakers). In addition, we collected continuous ratings on each of the 4 dimensions from 487 native English speakers. We performed mixed-effects regression analyses on RT and (mixed-effects logistic regression on) accuracy data. We found that size significantly predicts RT above and beyond these other more well-established semantic dimensions as well as interacts with them in complex ways. With respect to accuracy, while neither the main effect of semantic size alone nor the four-way interaction between all dimensions of interest were significant predictors, there were some significant two- and three-way interactions between size and the other semantic dimensions. Our findings suggest that semantic size of word stimuli impacts RT directly but also has a complex moderating effect with other semantic dimensions in both RT and accuracy.

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Poster

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Topic: H.11. Language

Support: Autism Speaks / Royal Arch Masons

Title: Neural and behavioral correlates of lexical repetition priming in autism, under interventional acoustic manipulation

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Abstract: Some autistic children have difficulty suppressing irrelevant sensory detail, compromising perceptual object formation. In real-time speech processing this may lead to delays in interactive communication or, more severely, difficulty establishing rudiments of a

language faculty, with downstream language impairment. Given autistic heterogeneity, this is likely not ubiquitous, but confined to a sub-population. If identified, it would conceptually lead to optimized support/treatment management. One example of suppressing meaning-irrelevant details is processing of speech from speakers with different acoustic parameters, e.g. pitch; thus, we developed a paradigm of modified repetition priming (RepPrim) in which listeners heard pairs of similar or different words. Words were either spoken by the same speaker or speakers with different pitch (M vs. F). The priming experiment examines the reaction time (RT) to the second word, which may be modulated by context (priming). Towards future intervention, we examined remediating M vs. F speaker differences with pitch shifting, raising the male utterance 7 semitones and lowering the female 5 semitones - approximately pitch equivalence. In 14 autistic children, 8-12yrs, we conducted this paradigm while undergoing MEG. Furthermore, we probed auditory processing using a 500Hz tone, focusing on the M50 component latency, reported to be delayed in autism. 13 exhibited canonical RepPrim - unprimed RT: 1.84±0.12s; RepPrim: 1.59±0.09s, $p<0.01$. With word pairs primed by a speaker of different pitch, RT responses identified two subtypes: (A) partial RT facilitation (n=8: unprimed RT: 1.99±.14s; RepPrim: 1.57±.11s, different pitch RepPrim: 1.58±.10s, $p<0.01$ vs unprimed) and (B) absent facilitation or even “distracted” RT delay (n=5: unprimed RT: 1.73±.21s, RepPrim: 1.61±.21s, different pitch RepPrim: 1.84±.24s, $p<0.01$ vs same speaker). In class B only, digital pitch manipulation led to normalization of RT: 1.53±.17s, $p=0.06$. While M50 latency exhibited typical hemispheric and developmental (~-8ms/yr, $p<0.05$) effects, there was no association of above class membership in a mixed model, suggesting acoustic hyperattention leading to delayed RTs was not in fact associated with auditory processing signatures. While simple auditory processing signatures such as M50 may not be effective screening tools to identify subpopulations of autistic children with delayed priming responses, such a population does exhibit dramatic normalization of RT priming effects upon pitch shifting of auditory input, perhaps paving the way for a new class of support/intervention potentially realizable in a hearing aid form factor.

Disclosures: T. Roberts: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proteus Neurodynamics, Fieldline Inc., Prism Clinical Imaging. F. Consulting Fees (e.g., advisory boards); WestCan proton therapy, Spago Nanomedicine. **M. Melch:** None. **L. Blaskey:** None. **C. Jackel:** None. **D. Embick:** None.

Poster

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Topic: H.11. Language

Support: NIH Grant 1P50HD105354

Title: Auditory evoked response latency associated with language in preschoolers with a higher likelihood of intellectual and developmental disability

Authors: *Y. CHEN[1], L. YOUNG[1], V. KAUFMAN[1], J. C. EDGAR[1,2], M. KIM[1], E. S. KUSCHNER[1,3], T. P. L. ROBERTS[1,2];
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Abstract: Research from our team has shown that a delayed auditory cortex neural response is associated with language ability in school-age children with autism spectrum disorder (ASD). As a clinical diagnosis of Intellectual and Developmental Disability (IDD) is often not made until school age, identification of neural measures that precede an IDD diagnosis would help identify young children likely to benefit from early treatment. It was hypothesized that the latency of auditory cortex neural activity would predict language scores in 3-year-old children with an elevated likelihood for an IDD diagnosis (IDD-EL). Evaluable magnetoencephalography (MEG) data and language performance measures were obtained from 18 children with IDD-EL (7 females; 2 years 8 months to 3 years 8 months). Auditory cortex activity in response to 500Hz sinusoidal tones was measured using MEG. Language measures were obtained using the Preschool Language Scale, Fifth Edition (PLS-5). **MEG P**rotocol for **L**ow-Language/Cognitive Functioning **A**bility **N**euroimaging model (MEG-PLAN) was used to optimize MEG data yield and improve the families' experience. MEG data were analyzed using Brainstorm software. Each child's MEG data were co-registered to an age-appropriate MRI template and then band-pass filtered from 3 to 55Hz. Physiological and non-physiological artifacts were removed using independent component analyses. Artifact-free whole-brain maps were computed using Minimum Norm Estimates (MNE). For each child, a left and right auditory cortex region of interest were identified, and left and right auditory source timecourses and M50 peak latency score obtained. Associations between left and right M50 latency and PLS total language score were examined. The Total Language Score (TLS) from the PLS-5 is used to identify children with and without language impairment. Of the 18 children (TLS standard score mean=83, standard deviation=28, range 50–128), 8 had a TLS below 85, indicating language impairment. Linear regressions showed that a later M50 latency was associated with a lower TLS in the left (R^2=0.24, p=.04) but not right hemisphere (R^2=0.00, p=.99). A longer time to encode auditory stimuli in the left hemisphere predicted poorer performance on a language test in preschoolers with a known higher likelihood for later IDD diagnosis. Present findings show that non-invasive brain imaging and a passive auditory task can identify mechanistic correlates for variable language outcome in young children with IDD-EL. This lays the foundation for examining these neural mechanisms as possible early indications for treatment.

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Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

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Title: Distinct recovery patterns of words and pseudowords from left-hemisphere stroke as revealed by geodesic clustering of functional connectivity

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Abstract: Language impairments (aphasia) following left-hemisphere stroke resolve to varying degrees from the acute to chronic epoch. Still unresolved are the roles of the left and right hemispheres in spontaneous recovery, and whether they reflect involvement of different linguistic information such as phonology (spoken word forms) or semantics (word meanings). Dynamic functional connectivity, which measures how synchronized patterns of brain activity change over time, allows us to capture dynamic changes in network reorganization and identify which neural areas are recruited for language post-brain damage.Nine patients with stroke-aphasia (M_{age}= 61.7, SD_{age}= 15.8; 5 females, 4 males) were tested in the acute (<4 weeks) and chronic (>3 months) epochs post stroke. They completed reading aloud tasks to measure reading accuracy. Words and nonwords were read to elicit semantic and phonological processing. We used machine learning to analyze task-based functional connectivity (t-FC) with a Riemannian manifold geometry-based approach. This method clustered dynamic t-FC matrices based on geodesic distance to identify distinct connectivity patterns for different stroke epochs (acute vs chronic) and conditions (word vs nonword). This approach has been shown to improve the predictive power of the machine learning classifiers. We extracted BOLD time-series data from the Glasser atlas parcels and computed the dynamic t-FC matrices with a sliding window of 40 TRs (176s) and step size of 6 TRs (24s), resulting in 445 t-FC 360x360 matrices. A vector representation was obtained by geodesic clustering of the dynamic t-FC matrices and computing the geodesic distance from each matrix to cluster centroids (i.e., reference connectome).Patients were more accurate in reading words (13% improvement) and nonwords (15% improvement) in the chronic phase than in the acute phase (corrected $p<.01$). Greater connectivity was found in the chronic phase, with more within-hemisphere connectivity for nonwords in both hemispheres, especially for medial structures related to speech and phonology such as the anterior cingulate/pre-supplementary motor area. More right-hemisphere connectivity in the chronic epoch was found for words. Results suggest that connectivity increases from the acute and chronic phases depending on what information is used to perform the task. When reading words in the chronic phase, individuals may engage the semantic system to pronounce meaningful words, taking advantage of the intact right hemisphere. When reading nonwords, participants engage both hemispheres, potentially leveraging what remains of their left-hemisphere phonological system.

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Poster

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Support: R01DC020965

Title: Dynamics of emotion processing in post-stroke aphasia: Insights from continuous valence ratings during naturalistic movie viewing

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Abstract: Aphasia, a language disorder caused by brain damage, affects an individual's ability to communicate effectively. Research suggests that investigating the link between language and emotional processing can provide valuable insights into the subjective experiences and challenges faced by persons with aphasia (PWA). The current study aimed to investigate the relationship of emotion and language processing dynamics in PWA compared to age-matched healthy controls (HC). We hypothesized that PWA would exhibit altered temporal dynamics and complexity of emotional processing compared to HC, and that these differences would be related to their language deficits.PWA (n=11; 3F, 8M; mean age=61.25,SD=6.9; mean aphasia severity=78.53, SD=17.13, range=42.1-98) and HC (n=33, 17F, 16M, mean age=54.58, SD=12.37) viewed 5-8 movie clips while providing continuous valence ratings via CARMA, a media annotation program. A subset of participants underwent eye-tracking. PWA completed a battery of standardized language and cognitive assessments. Intraclass correlation coefficients (ICC) were calculated to assess the reliability of valence ratings within each group. A maximal random-effect structure model was used to examine the contribution of aphasia severity to the variability in valence ratings in PWA. Multiscale sample entropy analysis was performed to compare the complexity of valence ratings between PWA and HC.ICCs of continuous valence ratings revealed good reliability across the PWA (ICC=0.815) and excellent reliability across the HC (ICC=0.905) groups. Variance decomposition of the maximal model showed that aphasia severity marginally contributed to the variability in valence ratings (~5%). Multiscale sample entropy analyses revealed significantly lower complexity of emotional responses for PWA versus HC in four movie clips ($p \leq 0.01$).The current findings suggest altered dynamics of emotional processing in aphasia, as evidenced by lower ICC and reduced complexity of valence ratings in PWA. Aphasia severity only marginally contributed to the variability in valence ratings for PWA, though aphasia type could importantly moderate this effect. Future analyses will further explore the relationship between valence ratings, eye-tracking metrics, and clinical

assessments to establish the interplay between language and emotional processing in aphasia and inform novel diagnostic and intervention strategies.

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Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.23/O33

Topic: H.11. Language

Support: TUM Innovation Network Neurotechnology in Mental Health

Title: Investigating word production errors in aphasia with Large Language Models and intracortical microelectrode recordings

Authors: *L. SCHIFFL[1,2], L. M. HELD[1,2], A. WAGNER[2], B. MEYER[2], J. GEMPT[3], S. N. JACOB[1,2];
[1]Translational Neurotechnology Laboratory, Dept. of Neurosurg., Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [2]Dept. of Neurosurgery, Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [3]Neurosurg., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: In contrast to impairments in speech articulation, for example in dysarthria, word production errors in patients with non-fluent aphasia stem from failure to select a conceptual representation, retrieve the corresponding lexical entry, and/or construct its phonological word form. Although the order of cognitive processes required to move from intention to articulation is generally accepted, their underlying temporal and spatial signatures have mainly been described in behavioral and electromagnetic studies lacking single-neuron resolution. In this case study, we investigate different types of naming errors in a patient with aphasia by combining the strength of speech and language embeddings from Large Language Models (LLMs) with the superior spatial and temporal resolution of intracortical microelectrode recordings (N=256 electrodes) from right-hemispheric brain regions homotopic to the left language system (inferior frontal gyrus, middle frontal gyrus, angular gyrus, supramarginal gyrus). After having demonstrated the involvement of all recorded areas in language processing in an accompanying study (“Right-hemispheric language processing at single-neuron resolution”, presentation by L. Held et al.), we focus here on the analysis of word production errors in a picture naming task. While linguistic features and word embeddings from LLMs are capable of capturing both the relations of target words to other words in the stimulus set (i.e., their semantic and syntactic categories, phonological minimal pairs) as well as the relations of target words to their output in speech (i.e., correctness, semantic distance, error type), the microelectrode recordings offer a unique opportunity to extend these relationships to the underlying single neuron activity. The

patient showed constant naming accuracies over the course of several months that varied for individual words and could be predicted by linguistic features as well as LLM embeddings. Preliminary analyses contrasting neuronal responses in correct naming trials, which involve successful retrieval and production of the target word, with responses in incorrect trials suggest that single units exhibit variations in spiking activity that are indicative of the patient's language output and specific for the recorded brain region. This study will serve to elucidate the fine-grained temporal and spatial characteristics of neuronal activity underlying word retrieval difficulties in aphasia.

Disclosures: L. Schiffl: None. **L.M. Held:** None. **A. Wagner:** None. **B. Meyer:** None. **J. Gempt:** None. **S.N. Jacob:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.24/O34

Topic: H.11. Language

Support: TUM Innovation Network Neurotechnology in Mental Health

Title: Right-hemispheric language processing at single-neuron resolution

Authors: *L. M. HELD[1,2], L. SCHIFFL[1,2], A. WAGNER[2], B. MEYER[2], J. GEMPT[3], S. N. JACOB[1,2];
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Abstract: The human language system is predominantly associated with the left hemisphere. Damage to left brain regions typically results in language disorders (aphasia). As patients regain language abilities, linguistic functions must redistribute to other brain regions, possibly to the right hemisphere. To gain an in-depth understanding of the right hemisphere's role in residual language following brain injury, we chronically implanted a patient with stroke-induced aphasia with four intracortical micro-electrode arrays (totaling 256 channels) in right-hemispheric regions homotopic to the left-hemispheric language network: the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supramarginal gyrus (SMG) and angular gyrus (ANG). Over several months, the patient performed single word repetition, comprehension and picture naming tasks while we recorded large-scale extracellular neuronal activity. In line with non-fluent aphasia, accuracy in comprehension and repetition tasks was high, yet low in naming. Activity patterns of single units in all implanted areas provided unequivocal evidence for their involvement in language processing with firing rate changes that were task-, event- and region-specific. In SMG, for example, neuronal activity following stimulus presentation varied as a

function of individual target words in particular in the naming task, but less so in the repetition or in the comprehension task. Because repetition and naming tasks entail similar articulatory processes, but differ fundamentally with regard to the involved word-retrieval processes, this finding supports a role for SMG in lexical access and phonological encoding. In IFG, for example, single units spiked predominantly during word production in the repetition task, but peaked earlier, before speaking, in the naming task. Fittingly, we find IFG activity to be informative about individual target words not only during speech production, but also before speech onset (i.e. during speech planning) in naming trials. Overall, this study lends unique insights into the right hemisphere's role in normal and impaired language processing as well as into the reorganization of language functions after stroke-induced brain injury.

Disclosures: L.M. Held: None. **L. Schiffl:** None. **A. Wagner:** None. **B. Meyer:** None. **J. Gempt:** None. **S.N. Jacob:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.25/O35

Topic: H.11. Language

Support: 5132100125 Nebraska Research Initiative

Title: Gesture Use in Parents of Children with Autism Spectrum Disorder During a 25 Minute Play Task

Authors: *P. LAI;
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Abstract: Children with Autism Spectrum Disorder (ASD) have significant social communication impairments that interfere with everyday life skills. According to the Centers for Disease Control and Prevention, ASD affects an estimated 1 in 36 children in the United States (Maenner et al., 2023). One area gaining attention in ASD research is the role of parents and their effectiveness in providing interventions and treatments to their child in their homes. This line of research is especially pertinent due to the current pandemic, where social distancing measures have severely impacted family's access and interactions with allied health professionals (Manning et al., 2020). There is a critical need for studies to investigate, for example, the effectiveness of social interaction by exploring variables from both the parents' and the child's perspective. This research included 12 children at ages 4-8. Of the 12 children, 5 children had a diagnosis of Autism Spectrum Disorder and 7 were typically developing (TD) children in the control group. During the session, one caretaker interacted with their child for about 25 minutes as we recorded the session. Parents were instructed to play with your child as you normally would at home using a standard set of toys. The toys (i.e., Mr. and Mrs. Potato Head and a Fisher-Price Farm Set) was provided for the task to all parents to maintain

consistency. Sessions were audio/videotaped for coding using EUDICO Linguistic Annotator software. Gestures were coded for any hand movement that had communicative intent. The coder of the gestures was blind to group identification. Results indicate more consistency in the numbers of gestures in the TD group as compared to the ASD group. In the ASD group, we had one parent and child pair with over 100 gestures and at the same time, another pair with just 19. This difference might be reflected in the type of gestures, as the parent with 103 gestures were constantly trying to engage with their child. Future research will explore if gestures are being used as a primary communicative channel or if gestures are used in conjunction with speech in both groups of children. In addition, gesture complexity will be evaluated to see not only the quantity, but the quality of gestures being produced.

Disclosures: P. Lai: None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.26/O36

Topic: H.11. Language

Support: Undergraduate Research Experience-Nebraska EPSCoR

Title: Verbal Output Differences in Fathers and Mothers When Interacting with their Child with Autism Spectrum Disorder

Authors: *M. DRIEWER, E. KRAFT, M. FORSBERG, P. T. LAI;
Communication Disorders, Univ. of Nebraska at Kearney, Kearney, NE

Abstract: Children with Autism Spectrum Disorder (ASD) have significant impairments in social communication that interfere with their personal and academic skills (Wood-Downie, Wong, Kovshoff, Cortese, & Hadwin, 2021). One of the first signs of atypical development noted by parents of children with ASD is delayed language development and communication (Lazenby et al., 2015). One area that is not well understood is whether certain aspects of communication (i.e., rate of verbal output, rate of gestures, physical contact) of the caretaker play a role in how language is expressed in children with ASD. In this study, we examined gestures, physical contact, and speech output by both the child and the caretaker to observe communicative behaviors during a 15-minute play session. This project specifically investigated verbal output during the social interaction. For this study, 17 parent-child pairs were investigated. All of the children in this study were diagnosed with Autism Spectrum Disorder and were between 2.5-5.5 years of age. These parent-child pairs engaged in a 15-minute dyadic play session. This project consisted of three behavioral coders; each coder was assigned 5-6 video files. Video data was coded in Eudico Linguistic Annotator (ELAN). This project coded for different aspects of communication of both the child and the caretaker with a focus on verbal attempts from both the parent and the child. Results suggest a pattern emerging in which we are

seeing a correlation between parents and their child's verbal attempts. When comparing fathers and mothers, fathers expressed more verbal output than mothers (M=185 vs. 169). In addition, we are seeing the child's verbal output mirroring the parent's output; the child is expressing more verbal attempts when speaking to the father than the mother (M=65 vs. 38). Taken together, a relationship between the child and their parent's communication patterns are emerging. Gesture and physical contact will be examined next, to see if this pattern observed in speech is also reflected in these two other communicative channels.

Disclosures: M. Driewer: None. **E. Kraft:** None. **M. Forsberg:** None. **P.T. Lai:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.27/O37

Topic: H.11. Language

Support: Undergraduate Research Experience-Nebraska EPSCoR

Title: Do Mothers and Fathers Have Similar Interaction Patterns With Their Child with Autism Spectrum Disorder?

Authors: *M. FORSBERG, M. DRIEWER, E. KRAFT, P. T. LAI;
Communication Disorders, Univ. of Nebraska at Kearney, Kearney, NE

Abstract: Children with Autism Spectrum Disorder (ASD) have significant impairments in social communication and social interaction. According to the Centers for Disease Control and Prevention (CDC), ASD affects an estimated 1 in 36 children in the United States (Maenner et al., 2023). This disorder is a growing public health concern as ASD occurs in all ethnic, racial, and socioeconomic groups (Fairthorne, de Klerk, Leonard, Schieve, & Yeargin-Allsopp, 2017). The lifetime total cost of ASD in the U.S. was estimated to be more than 7 trillion dollars in 2019 and is projected to cost 15 trillion dollars by 2029 if the prevalence rate continues to rise (Cakir, Frye, & Walker, 2020). In this study, we aim to determine if the gender of the parent will produce distinct communicative patterns when interacting with their child with ASD. For this study, 17 parent-child pairs were investigated. Of the 17 parents, 9 were fathers and 8 were mothers. These parent-child pairs engaged in a 15-minute play session. All children in this study were between 2.5 and 5.5 years of age. Video data were coded in Eudico Linguistic Annotator (ELAN). Two sets of toys were provided by the researchers, a Mr. & Mrs. Potato Head and a Little People Animal Sounds Farm set. Parents were instructed to "play with your child as you normally would at home." The focus of this project was on gestures of the child during a dyadic social interaction. Taken together, children interacting with their fathers averaged 27.44 gestures while 29.38 gestures were observed when interacting with the mothers. This result suggests that children with ASD are gesturing in relatively equal amounts regardless of which parent they are interacting with. This potentially can imply that the communication patterns we are observing are

largely driven by the family relationship of each pair. Future research will investigate family dynamics observing whether siblings of the child with ASD influences the communication patterns of parents.

Disclosures: M. Forsberg: None. **M. Driewer:** None. **E. Kraft:** None. **P.T. Lai:** None.

Poster

PSTR141: Language: Acquisition, Usage, Comprehension, and Impairment

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR141.28/P1

Topic: H.11. Language

Support: Undergraduate Research Experience-Nebraska EPSCoR

Title: Variability in Physical Contact During a Free-Play Task in Parent and Child with Autism Spectrum Disorder

Authors: *E. KRAFT, M. FORSBERG, M. DRIEWER, P. T. LAI;
Communication Disorders, Univ. of Nebraska at Kearney, Kearney, NE

Abstract: The overwhelming majority of parent-child research has involved mothers (Fang, Luo, Boele, Windhorst, van Grieken, & Raat, 2022). Historically, fathers have been underrepresented in research (Davison, Charles, Khandpur, & Nelson, 2017, Lindsay, Valdez, Pineda, & Muñoz, 2021). For example, in pediatric research, 48% of studies on parenting and child psychopathology included only mothers. In contrast, studies with data from only fathers came in at 1% (Phares, Lopez, Fields, Kamboukos, & Duhig, 2005). Interest in fathers as active parents has increased in recent years with considerable attention given to father involvement in direct child-rearing activities (Brown, McBride, Shin, & Bost, 2007). Gestures, physical contact, and speech output by both the child and the caretaker was investigated during a 15-minute play session. For this project, physical contact was researched between the parent and the child with ASD. Physical contact can be used as a communicative channel, especially when children are minimally verbal (Hazen & Black, 1989). For this study, 17 parent child pairs were investigated. All the children in this study were diagnosed with Autism Spectrum Disorder. These parent-child pairs engaged in a 15-minutes play session. All children in this study were between 2.5 to 5.5 years of age. This study uses archival data collected by the University of Wisconsin-Madison. The results for physical contact produced a trend, where fathers were averaging 20.33 instances of physical contact during the play session. On the other hand, mothers produced an average of 29 instances of physical contact during the dyadic social interaction. Taken together, we are beginning to see a trend in physical contact in our groups. In the future, we would like to add more participants in this study to make it more powerful. In addition, we would like to see if the gender of the child plays a role in how parents interact during a social interaction. Our next steps would be to look at emotional expression within the child to see if this behavior is influenced by physical contact with the parents.

Disclosures: E. Kraft: None. **M. Forsberg:** None. **M. Driewer:** None. **P.T. Lai:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.01/P2

Topic: H.13. Schizophrenia

Title: Network modulation of auditory event-related potentials in schizophrenia

Authors: *R. SHEWCRAFT;
Bristol Myers Squibb, Lawrenceville, NJ

Abstract: Impaired attention is recognized as a core cognitive symptom in individuals with schizophrenia (SZ). As a result, stimulus-evoked responses are reduced in SZ patients (Martinez et al. 2015). Attention enhances the synchronization and alignment of neuronal excitability dynamics, leading to the modulation of response gain and amplification of neuronal responses (Lakatos et al. 2008). Therefore, we hypothesized that patients with schizophrenia may have reduced modulation of neuronal responses to external stimuli.
To investigate this hypothesis, we examined auditory event-related potential (ERP) data in healthy controls (HC) and SZ patients (Ford et al. 2014) available on Kaggle. We analyzed data from the Play Tone task, where a series of 50ms auditory tones were presented at 1-2 second intervals to subjects who were passively listening. At the single trial level, both HC and SZ participants displayed variability in amplitude and latency of ERPs, with some trials showing no discernible deflection (misses) following stimulation. To determine ERP hit and miss trials, we employed an accumulated log-likelihood ratio method (Bannerjee et al. 2010).
The phase of ongoing EEG dynamics at the time of stimulus presentation predicts both the magnitude of neuronal response and likelihood of stimulus detection, suggesting that EEG phase is a signature of cortical excitability (Mathewson et al. 2009). Here, we show a difference in the depth of modulation in both HC and SZ groups, as indicated by the distribution of pre-stimulus phases for hit and miss trials. The probability of a hit was highest around the EEG trough. However, the difference in the mean of the pre-stimulus phase for hits and misses had different distributions (Watson's U^2, $p<0.05$) was greater for HC than SZ (Watson-Williams Test, $p=1.5x10^{-7}$), suggesting the depth of excitability-based modulation is greater in HC than in SZ patients.
The pre-stimulus phase difference for hit and miss trials was clustered around pi for HC (var = 0.67). However, for SZ the difference was more dispersed (var = 0.81). A simple threshold defined by pi/2 reveals two subsets. In one where the difference is small and predominantly SZ (78%). The remaining subset is more evenly mixed (47% SZ). This suggests that the depth of modulation of stimulus responses may be a biomarker for identifying SZ patients with attention deficits. Previous studies have indicated that attentional modulation is influenced by muscarinic receptor activation (Dasilva et al. 2019). Therefore, ERP-based measures of modulation depth

may prove to be useful markers for assessing functional responses to therapeutics targeting muscarinic receptors.

Disclosures: R. Shewcraft: A. Employment/Salary (full or part-time):; Bristol Myers Squibb. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bristol Myers Squibb.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.02/P3

Topic: H.13. Schizophrenia

Title: Excitatory-inhibitory dynamics in auditory cortex during hallucination-like perception

Authors: *K. FARRELL, A. VIDUOLYTE, K. SCHMACK;
The Francis Crick Inst., London, United Kingdom

Abstract: Hallucinations are a cardinal feature of psychosis, defined as the false perception of stimuli with the same confidence as veridical perception. People experiencing auditory hallucinations display elevated activity in auditory cortex (*Dierks et al., 1999; Shergill et al., 2000*) reflecting disrupted excitatory-inhibitory balance, but how this relates to false perceptions is unknown. One theory is that inhibitory interneuron activity is reduced, perhaps through hypofunction of the NMDA receptor, which disinhibits pyramidal neurons *(Homayoun and Moghaddam, 2007*). To understand the role that excitatory and inhibitory cortical neurons play in hallucinations, we leverage a dual-colour calcium imaging approach and chemogenetics in freely moving mice performing an auditory detection task that operationalises hallucination-like perception as high confidence false detections (*Schmack et al., 2021*).
Mice (N=14) learned to correctly detect a stimulus in white noise and report its presence in the auditory detection task, with detection probability and confidence scaling with signal volume. Mice exhibited a baseline level of hallucination-like perception instances where they reported hearing the stimulus with high confidence even though no stimulus was presented. To examine cortical dynamics during these trials, we performed dual-colour calcium imaging using a Miniscope (N=4) in order to quantify the activity of pyramidal neurons and parvalbumin-positive (PV+) interneurons in auditory cortex. Preliminary data indicates that pyramidal neurons exhibit stimulus responses that are modulated by volume, but do not exhibit stimulus-like responses in the absence of stimulus, even on hallucination-like perception trials. Administration of ketamine, a NMDA receptor antagonist, selectively increased high confidence hallucination-like perceptions and modulated neuron activity, supporting the idea that NMDAR hypofunction is a mechanism for hallucinations in psychosis. Preliminary data also suggest that chemogenetic inhibition of PV+ interneurons (N=6) increased false perception, supporting the idea that reduced inhibition may contribute to psychotic symptoms. Ongoing experiments are investigating whether chemogenetic activation of PV+ interneurons is sufficient to reduce false perceptions

and rescue the effect of ketamine on hallucination-like perception. Taken together, our preliminary results indicate a role for auditory cortex excitatory-inhibitory dynamics in hallucination-like perception and provide a promising avenue for examining how excitatory-inhibitory imbalance and NMDAR hypofunction are related to hallucinations.

Disclosures: K. Farrell: None. **A. Viduolyte:** None. **K. Schmack:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.03/P4

Topic: H.13. Schizophrenia

Title: Enhanced in vivo firing of substantia nigra dopamine neurons projecting to the dorsal striatum in the Df(16)A$^{+/-}$ mouse model of schizophrenia

Authors: *S. BIKAS, P. VOGEL, A. DIAMANTOPOULOU, J. ROEPER;
Inst. of Neurophysiology, Goethe Univ., Frankfurt am Main, Germany

Abstract: The region-specific elevation of dopamine (DA) levels in the associative striatum of non-medicated patients with schizophrenia (SCZ) has been a key finding regarding the pathophysiology of the DA system of this disease. It is however unknown, whether this respective DA system is also preferentially affected in any model system. Given that the 22q11.2 microdeletion carries the largest known genetic risk for SCZ, we studied a genetically modified mouse model carrying a hemizygous chromosomal deletion on chromosome 16 (*Df(16)A*$^{+/-}$), which is syntenic to the human 22q11.2 locus. Initially, we characterized *in vivo* properties of pharmacologically identified, putative DA midbrain neurons by chronic *in vivo* single-unit extracellular recordings during open field exploration in awake, freely moving *Df(16)A*$^{+/-}$ mice and littermate controls. We detected about 50% persistently increased firing frequencies for DA neurons in the medial substantia nigra (mSN) in both male and female *Df(16)A*$^{+/-}$ mice in comparison to controls (male: WT FR: 5.15 Hz, n=84, N=6; *Df(16)A*$^{+/-}$ FR: 7.84 Hz, n=130, N=7; 1.5–fold; $p = 0.0001$; female: WT FR: 5.05 Hz, n=95, N=6; *Df(16)A*$^{+/-}$ FR: 8.06 Hz, n=95, N=5; 1.5–fold; $p < 0.0001$). A similar degree of hyperactivity was also observed in putative DA neurons recorded in the lateral SN of male *Df(16)A*$^{+/-}$ mice (WT FR: 6.51 Hz, n=49, N=7; *Df(16)A*$^{+/-}$ FR: 9.75 Hz, n=52, N=7; $p = 0.0077$). In contrast, no differences in firing rates were detected in recordings of putative DA neurons in the VTA between *Df(16)A*$^{+/-}$ and controls. To identify projection-specific DA subpopulations *in vivo*, we applied a AAV9-based retrograde tracing protocol to selectively express the inhibitory DREADD hM4D(Gi) in DA SN subpopulations in *DAT-Cre*$^{+/-}$ X *Df(16)A*$^{+/-}$ double transgenic mice. Retrogradely tagged SN DA neurons were identified by an inhibitory response (>50%) to the DREADD agonist Deschloroclozapine (100 µg/kg). This approach showed a 50% higher firing rate in identified dorso-medial striatum (DMS)-projecting DA SN neurons in *DAT-Cre*$^{+/-}$ X *Df(16)A*$^{+/-}$ mice compared to controls (DMS: *DAT-Cre*$^{+/-}$ FR: 4.94 Hz n=26, N=6; *DAT-Cre*$^{+/-}$ X *Df(16)A*$^{+/-}$ FR:

7.54 Hz, n=49, N=7; 1.52–fold; p = 0.0002). In contrast, identified DLS-projecting DA SN neurons displayed only a 25% higher firing rate in *DAT-Cre*$^{+/-}$ X *Df(16)A*$^{+/-}$ mice compared to controls (DLS: *DAT-Cre*$^{+/-}$ FR: 8.02 Hz n=42, N=7; *DAT-Cre*$^{+/-}$ X *Df(16)A*$^{+/-}$ FR: 10,13 Hz, n=39, N=7; 1.26–fold; p = 0.0358). Our findings provide robust evidence for a preferentially enhanced DA firing activity in DMS-projecting DA SNc neurons. Thus, the *Df(16)A*$^{+/-}$ mice might be suitable to study the molecular and cellular mechanisms for regional DA dysfunction in SCZ.

Disclosures: S. Bikas: None. **P. Vogel:** None. **A. Diamantopoulou:** None. **J. Roeper:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.04/P5

Topic: H.13. Schizophrenia

Support: NIH Grant R01 NS122840
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Title: Differential roles of D1 and D2 spiny projection neurons in cognitive symptoms of schizophrenia

Authors: *A. KANE[1,2], N. A. MOYA[1], J. G. PARKER[1];
[1]Dept. of Neurosci., [2]Northwestern Univ., Chicago, IL

Abstract: Schizophrenia is a complex neurological disorder with three symptom classes: positive, negative, and cognitive. Two of these classes, negative and cognitive, are notoriously difficult to treat. Elevated dopamine activity in the nigrostriatal pathway targeting the dorsal striatum is associated with positive symptoms, typically including hallucinations and delusions. Existing anti-psychotic medications treat positive symptoms by antagonizing striatal D2 dopamine receptors (D2Rs). However, cognitive symptoms like disruptions in working memory persist. Current anti-psychotics do not target D1Rs, another major subclass of striatal dopamine receptors, indicating a potential mechanism for these treatment-resistant symptoms. We propose that increased dopamine activity targeting D1R-expressing neurons drives cognitive symptoms. We developed a model of abnormal dopamine activity seen in schizophrenia patients by re-expressing the TRPV1 excitatory cation channel in the substantia nigra pars compacta (SNc) of *Trpv1* knockout mice. Further, we chemogenetically manipulated D1R and D2R spiny-projection neuron (SPN) activity to determine the effects of normalizing dopamine activity on each receptor. Administration of TRPV1 agonist capsaicin drove increased nigrostriatal dopamine release and hyperlocomotion in an open field arena, an indirect measure of positive symptoms. Capsaicin treatment impaired cognitive function in a T-maze working memory task, a cognitive

symptom assay [1]. Our tangential chemogenetic (DREADD) manipulation of D1 and D2-SPN activity clarified the causal roles of altered dopamine signaling in cognitive symptoms. Chemogenetic activation of striatal D2-SPNs partially reduces cognitive deficits produced by capsaicin injection. Further studies of neural activity in these regions and contributions from other regions, including the prefrontal cortex, are underway. Ultimately, we intend to identify specific targets for therapeutics to treat treatment-resistant symptoms of schizophrenia.References[1] Moya, N. A., Yun, S., Fleps, S. W., Martin, M. M., Nadel, J. A., Beutler, L. R., . . . Parker, J. G. (2022). The effect of selective nigrostriatal dopamine excess on behaviors linked to the cognitive and negative symptoms of schizophrenia. *Neuropsychopharmacology*, *48*(4), 690-699. doi:10.1038/s41386-022-01492-1

Disclosures: A. Kane: None. **N.A. Moya:** None. **J.G. Parker:** None.

Poster

PSTR142: Schizophrenia Circuits

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Program #/Poster #: PSTR142.05/P6

Topic: H.13. Schizophrenia

Support: NIMH F31 MH134549
NIH 2T32 MH067564
NINDS R01 NS122840
Whitehall Foundation

Title: The role of nigrostriatal and striatal cell subtype signaling in behavioral impairments related to schizophrenia

Authors: *N. A. MOYA, S. YUN, J. D. ANAIR, J. G. PARKER;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: Excess nigrostriatal (NS) dopamine signaling is linked to the positive symptoms of schizophrenia, which are mainly responsive to antipsychotic drugs that block D2 dopamine receptors (D2Rs). By contrast, cognitive symptoms are largely resistant to these same treatments. This observation fueled the dogma that excess striatal dopamine is not involved in cognitive symptoms. However, the striatum also expresses D1 dopamine receptors (D1Rs), which are not targeted by current antipsychotics. Therefore, increased NS dopamine transmission may contribute to cognitive symptoms through its actions on striatal D1R signaling, an idea that has never been directly tested. We asked whether striatal D1R- and D2R-expressing spiny projection neurons (SPNs) differentially contribute to dopamine-driven deficits in cognitive function. To do this, we developed an approach to mimic the pathway-specific excess in dopamine observed in schizophrenia by selectively expressing the excitatory cation channel TRPV1 in SNc dopamine neurons of *Trpv1* knockout mice. Systemically treating these mice with the TRPV1 agonist capsaicin increased dopamine release in the striatum and induced hyperlocomotion, but also

disrupted working memory, a behavioral proxy for cognitive symptoms (Moya *et al*., 2022). We are currently using this TRPV1-based approach with miniature microscopes to image Ca^{2+} activity in D1- or D2-SPNs under normal and hyperdopaminergic conditions to determine how altered activity in each SPN type may differentially contribute to cognitive deficits. We found that driving NS dopamine transmission with capsaicin decreases D2-SPN Ca^{2+} activity during periods of movement, and increases D1-SPN Ca^{2+} activity during rest in an open field. During working memory maintenance, subpopulations of both D1- and D2-SPNs encode choice direction and may encode prospective choice. We are currently refining the analyses of D1-SPN dynamics to determine their role in cognitive function. By defining the roles of striatal D1- and D2-SPNs in dopamine-driven changes in behavioral constructs related to schizophrenia, these experiments have the potential to identify novel therapeutic strategies for psychosis that more comprehensively address its symptoms.

Disclosures: N.A. Moya: None. **S. Yun:** None. **J.D. Anair:** None. **J.G. Parker:** None.

Poster

PSTR142: Schizophrenia Circuits

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Topic: H.13. Schizophrenia

Support: MRC Programme Grant
Marie Skłodowska-Curie

Title: Understanding the contribution of cortical interneuron dysfunction to schizophrenia

Authors: *F. WINKEL, D. MUKHERJEE, B. RICO, O. MARIN;
Ctr. for Developmental Neurobiology, MRC Ctr. Neurodevelopmental Disorders, King's Col. London, London, United Kingdom

Abstract: Schizophrenia is an incurable disease hallmarked by positive, negative, and cognitive symptoms. Currently, antipsychotic drugs are used to treat positive symptoms, including psychosis, but fail to alleviate cognitive and negative symptoms. Psychosis is associated with striatal hyperdopaminergia, hypothesized to be caused by abnormal activity of midbrain dopamine neurons. Dopamine levels are elevated before the onset of psychosis, suggesting that increased dopamine might be secondary to other alterations occurring earlier in life, for example, disruption of cortical circuits. *ERBB4* mutations have been linked to schizophrenia and other developmental conditions. Deletion of *Erbb4* from parvalbumin-expressing (PV) interneurons in the cortex and striatum reduces the excitatory synapses these neurons receive. Conditional *Erbb4* mouse mutants display a schizophrenia-like phenotype, including cognitive dysfunction and increased hyperlocomotion, the latter being associated with elevated dopamine levels in the striatum. Here, we investigated the mechanisms driving these alterations. We found that conditional *Erbb4* mutants exhibit striatal hyperdopaminergia, which is normalized by treatment

with D1 and D2 receptor antagonists. Medium spiny neurons receive fewer inhibitory synapses than control mice and exhibit increased Fos expression. Finally, regional deletion of *Erbb4* exclusively from neocortical PV interneurons is sufficient to cause hyperlocomotion, whereas deletion of *Erbb4* from striatal interneurons has a minor influence on this phenotype. These results suggest that cortical PV interneurons are the primary driver of schizophrenia-like phenotypes in conditional *Erbb4* mutants. Our findings indicate that dysregulated interneurons in the neocortex are sufficient to induce changes that resemble the most prominent phenotypes observed in schizophrenia patients.

Disclosures: F. Winkel: None. **D. Mukherjee:** None. **B. Rico:** None. **O. Marin:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.07/P8

Topic: H.13. Schizophrenia

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Brain and Behavior Research Foundation Grant 30854
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Title: Linking dopamine dysregulation during adolescence and vulnerability to schizophrenia in a mouse model

Authors: *K. OTOMO[1], J.-F. POULIN[2], M. A. LABOUESSE[1];
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Abstract: Epidemiological data suggests that 0.5-1% of adults worldwide are diagnosed with schizophrenia, impacting the emotions, thought processes, and reality perception of those affected. Typically, schizophrenia onset occurs from late adolescence to early adulthood, with genetic and early-life environmental factors implicated in its strongly neurodevelopmental origin. The dopamine system plays a central role in schizophrenia, where dopamine 2 receptor antagonists serving as the first line of treatment since the 1950s. Numerous imaging studies highlight abnormal dopamine functions in schizophrenia patients, particularly increased striatal dopamine. Importantly, elevated striatal dopamine is a known predictor of future schizophrenia diagnosis and disease trajectory in young, at-risk individuals. Moreover, factors with a strong epidemiological link to schizophrenia, such as maternal infection, childhood adversity, and adolescent substance use, can impact the developing dopamine system, making it a converging point of schizophrenia pathologenesis. This has led to the hypothesis that elevated dopamine

signaling during development may lay the foundation for schizophrenia. Given evidence that periadolescent dopamine activity shapes striatal neuronal circuits, perturbation to this system during brain maturation may create vulnerability to schizophrenia-like manifestations in adulthood - a hypothesis tested in this study. Our initial in vivo fiber photometry experiments in mice show that exposure to stress or drugs of abuse elevates dopamine levels in the dorsal striatum. Based on this finding, along with insights from human studies, we developed a circuit-based mouse model where striatal dopamine is artificially elevated during adolescence. Using this new model, we demonstrate that excess dopamine during adolescence promotes behavioral phenotypes relevant to schizophrenia. We are currently investigating potential cellular mechanisms within the nigrostriatal pathway that may underlie these effects.

Disclosures: K. Otomo: None. **J. Poulin:** None. **M.A. Labouesse:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.08/P9

Topic: H.13. Schizophrenia

Title: The role of striatal acetylcholine in hallucination-like perception

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Abstract: Hallucinations, a cardinal feature of psychosis, are perceptions not grounded in external reality. Whilst the exact mechanisms of these experiences remain elusive, recent clinical trials of novel antipsychotic treatments suggest a link between the neuromodulator acetylcholine and psychotic symptoms. Notably, acetylcholine is abundant in the striatum where it can interact with dopamine, a neuromodulator known to be elevated during psychosis. This suggests that striatal acetylcholine might play a crucial role in hallucinations. Here, we aimed to elucidate how striatal acetylcholine is involved in unfounded perceptions in mice and its interplay with dopamine.
To measure hallucinations in mice, we employed the recently established hallucination-like perception (HALIP) task (Schmack et al., 2021). In this task, mice are trained to report presence or absence of a tone embedded in a noisy background and express confidence in their decision by waiting for a reward. A hallucination-like percept is defined as a false alarm perceived with high confidence. We use dual-colour fiber photometry to measure the temporal dynamics of both acetylcholine and dopamine in mouse auditory striatum (N = 6) during hallucination-like perceptions.
We found that both acetylcholine and dopamine showed robust yet different responses to reward delivery, suggesting that our dual-colour approach successfully measured both neurotransmitters simultaneously. The signals of the two neuromodulators exhibited a multiphasic anti-correlated relationship, in line with previous observations in other striatal regions. Our preliminary results

further indicate differences in acetylcholine signal between false alarms and correct rejections during the period surrounding stimulus presentation, pointing to a role of acetylcholine in hallucination-like perception. To test the causality of acetylcholine's involvement in this behaviour, ongoing experiments employ chemogenetic inhibition of cholinergic neurons in the auditory striatum.
Together, these preliminary results suggest that altered acetylcholine transmission might give rise to hallucination-like experiences in mice. This paves the way for untangling the neural mechanisms by which novel antipsychotic treatments might take their effect.

Disclosures: A. Viduolyte: None. **K. Farrell:** None. **M. Bazley:** None. **K. Schmack:** None.

Poster

PSTR142: Schizophrenia Circuits

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Program #/Poster #: PSTR142.09/P10

Topic: H.13. Schizophrenia

Support: R01MH122545

Title: Pharmacological Modulation of Muscarinic M4 Receptors Reduces Spontaneous Striatal Dopamine and Acetylcholine Release

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[2]Pharmacology, Physiol. & Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Schizophrenia is a psychiatric disorder characterized by three clusters of symptoms: positive, negative, and cognitive. Patient brain imaging studies indicate that hyperdopaminergic signaling in the dorsal striatum plays a pivotal role in the etiology of this disorder, particularly in positive symptoms. Consistent with this hypothesis, a common feature of all current antipsychotic medications is modulation of dopamine D2 receptor activity. However, these medications may offer only partial relief from positive symptoms and do little to address other symptom clusters. This incomplete efficacy, coupled with a range of debilitating side effects, necessitates a need for improved antipsychotic therapies. One novel strategy under investigation is to target muscarinic receptors of the cholinergic system. The muscarinic M4 acetylcholine receptor represents a promising new drug target, and compounds targeting these receptors have the potential to be the first approved therapies lacking pharmacological activity at D2 dopamine receptors. However, the mechanism whereby drugs targeting M4 receptors can mediate antipsychotic effects is not fully characterized. Studies using microdialysis, phMRI, voltammetry, and brain slice physiology have shown that M4 PAMs can robustly modulate striatal physiology by inhibiting the release of numerous neurotransmitters, including glutamate, dopamine (DA), and acetylcholine (ACh). How M4 PAMs modulate release of these transmitters *in vivo*, however, is not well characterized with high temporal resolution. To this end, we utilized

fiber photometry approaches with fluorescent protein-based sensors for DA (dLight) and ACh (GRAB-ACh) to study how M4 receptors regulate spontaneous DA and ACh release *in vivo* at a subsecond timescale. We first obtained dose-response curves to assess M4 PAM (VU0467154) mediated changes in striatal ACh and DA release in awake-behaving animals. M4 PAMs were observed to reduce both striatal DA and ACh release event amplitudes without altering the frequency of events. This agrees with previous studies showing that muscarinic receptors can reduce DA release via numerous mechanisms and reduce ACh via M4 autoreceptor activation. Additionally, experiments are underway to assess M4 PAM-mediated effects on neurophysiological alterations induced by NMDA receptor antagonist MK-801 and the stimulant amphetamine and compare these responses to behavioral effects indicative of antipsychotic-like efficacy. Collectively, these studies will continue to elucidate how M4 PAMs modulate striatal physiology and help determine the mechanisms that are critical to their antipsychotic-like efficacy.

Disclosures: D.G. Joyner: None. **C.M. Johnston:** None. **Y. Choi:** None. **D.J. Foster:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.10/P11

Topic: H.13. Schizophrenia

Title: Muscarinic receptor (M1 and M4) modulation of gamma-frequency oscillations in the mouse hippocampus

Authors: S. A. NEALE[1], B. DENNIS[2], F. E. LEBEAU[2], *T. E. SALT[3,1];
[1]Neurexpert Limited, Newcastle Upon Tyne, United Kingdom; [2]Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]Univ. Col. London, London, United Kingdom

Abstract: Clinical evidence suggests muscarinic receptor modulators may alleviate the symptoms of schizophrenia. Aberrant oscillatory activity could be related to the core symptoms of schizophrenia such as hallucinations, thought disorders, negative symptoms and cognitive dysfunction. We have therefore evaluated muscarinic receptor modulators for effects on gamma-frequency activity recorded in the CA3 region of the hippocampus.
Hippocampal slices (horizontal, 450 µm) were prepared from anaesthetised mice (male, 8-12 weeks). Application of kainate (KA; 100 nM) alone, or KA (50 nM) plus carbachol (CCH; 5 uM) induced slow gamma frequency (20-30 Hz) oscillations that stabilised over 1-3 h of recording. Addition of the muscarinic antagonist scopolamine resulted in a concentration-dependent attenuation of the oscillations evoked by the KA/CCH combination. At the lowest concentration tested (0.1 uM; n=7) the amplitude of the oscillation was reduced to 35±4% ($P < 0.0001$) and the area under the curve (AUC) was reduced to 55±7% ($P < 0.001$). At the highest concentration tested (10uM; n=4) the amplitude was reduced to 19±7% ($P < 0.01$) and the AUC was reduced to 32±8% ($P < 0.01$). The peak frequency was not modulated. In contrast, addition of scopolamine

(10 uM) to KA-evoked oscillations did not modulate any of the 3 parameters. Addition of the subtype-selective M1 antagonist VU0255035 (5 uM; n=7) to slices treated with KA/CCH reduced both the amplitude and AUC of the oscillations to 18±4% ($P < 0.0001$), and 36±5% ($P < 0.0001$) respectively, without affecting peak frequency.
M4 receptor modulators are in development for the treatment of schizophrenia. We thus evaluated the M4-selective positive allosteric modulator VU10010 (5 uM) for effects on oscillations evoked by KA/CCH and by KA alone. After 20 minutes application of VU10010 the AUC of the oscillation evoked by KA/CCH was increased to 111±5% (n=8; $P < 0.05$). After an hour of application the AUC was still increased; on washout of VU10010 the AUC returned to baseline levels. In KA-evoked oscillations, VU10010 also increased the AUC to 112±5% (n = 10) after 20 mins of application. In contrast to the KA/CCH oscillation, the change in AUC did not recover on washout; instead, a secondary increase to 160±30% of baseline values after 60 mins was seen.
These data provide further evidence that muscarinic receptor ligands modulate ongoing network activity relevant to psychiatric conditions such as schizophrenia. Additionally, the data demonstrate the value of in vitro brain slices for evaluating the action of putative therapeutic agents on physiological network activity.

Disclosures: S.A. Neale: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Ltd. **B. Dennis:** None. **F.E. LeBeau:** 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.; Neurexpert Ltd. **T.E. Salt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurexpert Ltd.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.11/P12

Topic: H.13. Schizophrenia

Support: Stanley Center for Psychiatric Research at the Broad Institute

Title: Noradrenergic modulation of the prefrontal cortex is impaired in Grin2a mutant mice

Authors: H. HOSSEINI, *K. S. JONES;
Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: Schizophrenia is characterized by profound cognitive deficits, particularly in executive functions, which remain largely unaddressed by current pharmacological treatments. Recent research has implicated the *GRIN2A* gene—which encodes the GluN2A subunit of the N-

methyl-D-aspartate receptor (NMDAR)—as a significant risk factor in schizophrenia. This finding suggests that loss-of-function mutations in *GRIN2A* may disrupt neural circuit functions crucial for cognition. The medial prefrontal cortex (mPFC) is a critical hub for cognition and is strongly modulated by noradrenaline (NE). In this study, we utilized Grin2a mutant mice to explore the role of NE in mediating oscillatory activity within the mPFC. We employed optogenetic stimulation of locus coeruleus-noradrenergic (LC-NE) terminals in ex-vivo mPFC slices. We used planar multi-electrode array and patch-clamp electrophysiology to monitor the resultant neural activity, namely high-frequency oscillations (HFOs) and theta-gamma phase-amplitude coupling (PAC). HFOs are rapid neural oscillations associated with cognitive processing and memory formation. Phase-amplitude coupling (PAC) is a mechanism thought to coordinate neural communication and cognitive processes across the brain, and theta-gamma phase-amplitude coupling (PAC) is crucial for coordinating cognitive processes. Aberrant HFOs and PAC, common in schizophrenia, likely reflect underlying neural disruptions. Aberrant HFOs and PAC are observed in schizophrenia patients, potentially reflecting the underlying disruptions in neural circuitry that contribute to cognitive deficits. Our results indicate that NE significantly enhances HFO power in wild-type mice (98.3 %, SD: 35.0 %), compared to heterozygous and knockout *Grin2a* mutants (HET: 30.8%, SD: 27.1%; KO: 76.8%, SD: 23.8%; $F=12.4$, $p=0.00022$). Furthermore, NE's role in strengthening PAC was found to be dependent on the function of GluN2A-containing NMDARs, a finding that we confirmed in WT tissue using subunit-selective NMDAR antagonists. Our findings suggest that disruptions in NE signaling and GluN2A functionality could underlie some of the cognitive deficits observed in schizophrenia, offering potential targets for therapeutic intervention. This research advances our understanding of the neurophysiological mechanisms underlying schizophrenia and provides a foundation for the development of novel treatments aimed at restoring cognitive function in affected individuals.

Disclosures: H. Hosseini: None. **K.S. Jones:** None.

Poster

PSTR142: Schizophrenia Circuits

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Topic: H.13. Schizophrenia

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Alberta Graduate Excellence Scholarship, University of Alberta
Graduate Research Assistantship Fellowship, University of Alberta

Title: Assessing cognition and mesoscale brain activity after perineuronal net degradation in the retrosplenial cortex

Authors: *A. THRAYA[1,2], J. W. PAYLOR[1,2], R. ZAHACY[2], J. G. HOWLAND[3], Y. MA[1], F. DE WINTER[4], J. VERHAAGEN[5], I. R. WINSHIP[1,2], A. W. CHAN[1,2];
[1]Psychiatry, [2]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [3]Dept. of Anatomy, Physiology, and Pharmacol., Univ. Saskatchewan, Saskatoon, SK, Canada; [4]Lab. for Neuroregeneration, [5]Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: The retrosplenial cortex (RSC) plays a crucial role in cognitive processes and has exhibited impairments in schizophrenia. Research has demonstrated its importance in working memory and the impact of structures called perineuronal nets (PNNs) in its function. These extracellular matrix components, mostly surrounding parvalbumin-positive interneurons (PV+), are key to neuronal organization and stability, regulation of synaptic plasticity and cognitive performance. Given their significance and their marked deficiency in schizophrenia, our study explores the effects of PNN depletion using Chondroitinase ABC (ChABC) within the RSC on working memory and brain activity.
We used a cohort of 35 mice (control, n=17; ChABC/dox+, n=18), from both sexes, approximately 2-months old, crossbred from two genetic strains (Thy1-GCaMP6S and Pvalb-tdTomato) on a BL6 background. An immune-evasive viral vector, dox-i-ChABC, enabled localized PNN degradation in the RSC, triggered by a doxycycline diet. Behavioral assessments were conducted at baseline, 1 month post-ChABC expression, and 1 month after cessation. Tissue samples for immunostaining of PV+ cells, PNNs, and chondroitin-sulfate proteoglycans were collected at 30 and 60 days post-treatment. Cortical activity was assessed by mesoscale calcium imaging (n=11). Investigators conducting behavioral and imaging tests were blind to the treatment status of mice.
Behavioral tests including the open field, spontaneous alternation, and oddity object recognition tests showed no significant changes in general motor activity or primary working memory functions. However, ChABC-treated mice demonstrated a significant increase in exploration time at the 30-day evaluation ($t(26)=2.684$, $p=0.042$) and reduced low-frequency (0.1-1 Hz) resting-state activity. Immunostaining revealed a 43.5% increase in cleaved PNN components and significant reductions of 28.8% in intact PNNs and 56.5% in PV+ interneurons after 60 days. Our data shows that 30 days of PNN degradation within the RSC can have a subtle impact on working memory and reduce the density of PV+ interneurons. Notably, PNN depletion altered exploration times which might suggest that these impairments are driven in part by changes in exploratory activity, rather than working memory impairment alone. Additionally, there was a significant reduction in spontaneous slow-wave activity after 30 days of ChABC expression, suggesting that further investigation into microscale cellular alterations after PNN degradation is required to help translate these broader cortical and cognitive results.

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Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.13/Q2

Topic: H.13. Schizophrenia

Title: The effects between physical activity and distressful psychotic-like experiences on canonical resting-state networks in youth

Authors: *A. BARRY[1], B. BARAN[2];
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Abstract: Physical activity has been shown to influence several aspects of brain function including cognition, psychopathology and brain connectivity. Of particular interest for the present study is psychotic like experiences (PLEs), which are subthreshold positive symptoms (i.e. unusual perceptions, thoughts or beliefs) that may increase risk for psychotic disorders. Previous work has demonstrated a link between physical exercise and PLEs, however the mechanism for this relationship is unclear. The goal of the present study was to test whether physical activity and PLE severity predicted resting-state functional connectivity networks in youth. Utilizing the Adolescent Brain Cognitive Development (ABCD) study, participants were selected from the 2ndyear visits who have completed MRI and mobile technology assessments (n=5954, 10-13 yrs, 47% female). Daily activity was defined as average number of daily steps measured over 9 weeks with Fitbit wrist watches. PLEs were calculated as the total distress score from Prodromal Questionnaire - Brief Child Version (PQ-BC). Functional connectivity analyses focused on within and between network relations of the Default Mode Network (DMN), Frontoparietal Network (FPN) and Salience Network (SN). Linear mixed-effects (LME) models were utilized to predict functional connectivity with factors for PLEs, physical activity, age, sex, BMI and household income and a random effect for sibling status. We replicated previous work by finding significant relations between PLEs and physical activity (r= -.08 , p<.0001). We observed a significant interaction between PLEs and physical activity that predicted within network DMN connectivity [F(1,5917.37) = 4.69, p = 0.03] such that physical activity was strongly and negatively associated with DMN connectivity only in children with high levels of distressing PLEs. Physical activity predicted DMN-FPN connectivity [F(1,5808.19) = 6.60, p = 0.01] such that more physical activity was inversely related to connectivity, and SN within network connectivity [F(1, 5765.80) = 7.97, p < 0.005] such that SN connectivity increased with physical activity. These findings reflect differential vulnerability in children with high levels of PLEs on Default Mode Network connectivity. While in the general population, higher physical activity relates to higher DMN connectivity, this relationship was reversed in youth with high PLEs. Future analytical plans include incorporating other measures of physical fitness (e.g. resting heart rate) and sleep quality.

Disclosures: A. Barry: None. **B. Baran:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR142.14/Q3

Topic: H.13. Schizophrenia

Support: CIHR

Title: Pathophysiology of retrosplenial cortex associated with cognitive impairment in mouse models of schizophrenia

Authors: *H. DOOSTI[1], M. V. BANDET[2], I. R. WINSHIP[3];
[1]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [2]Dept. of Psychiatry & Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [3]Neurosci. and Mental Hlth. Inst., Univ. Alberta, Edmonton, AB, Canada

Abstract: Schizophrenia (SCZ) is a severe, chronic illness that manifests with psychopathology that include positive, negative, and cognitive symptoms. Cognitive impairment in SCZ is debilitating and associated with substantial disruptions in the default mode network (DMN). As a heavily interconnected brain region and a major node of the DMN, retrosplenial cortex (RSC) is involved with a range of cognitive functions including memory and spatial navigation. While SCZ-related alterations in DMN regions in corresponding to over-activated microglia, brain-resident macrophage, has been described, dysfunction in RSC at the cellular and network level in SCZ has not been well defined. Here male and female C57/BL6 wild-type animals were treated with acute or chronic (14 days) treatment with ketamine (30 mg/kg, or control). Our data revealed that acute and chronic ketamine regimens impaired spatial and non-spatial cognitive ability in a sex-dependent manners, respectively. To relate impairments to alterations in neuronal and microglial physiology, in vivo two-photon as well as confocal microscopy were employed, respectively. Coincident with the behavioral results, our imaging data obtained from acutely and chronically treated Thy1-GcAMP6s transgenic mice showed sex-dependent distortions in neuronal spiking patterns concomitant with inhibitory network alterations in the RSC. Significant activation of microglial cells was accompanied by a decrease in perineuronal nets (PNNs) enwrapping parvalbumin-expressing interneurons in RSC following chronic treatment. Future experiments will define neuronal and inhibitory network activity alterations associated with the activation of microglial cells in RSC.

Disclosures: H. Doosti: None. **M.V. Bandet:** None. **I.R. Winship:** None.

Poster

PSTR142: Schizophrenia Circuits

Location: MCP Hall A

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Program #/Poster #: PSTR142.15/Q4

Topic: H.13. Schizophrenia

Support: T32-MH018870

Title: Utilizing widefield calcium imaging to evaluate activity and network connectivity in wildtype and schizophrenia genetic risk model mice

Authors: A. DORAN[1], *E. PARKER[1], D. S. PETERKA[2], J. A. GOGOS[1];
[1]Zuckerman Inst. for Mind, Brain and Behavior, [2]Zuckerman Inst., Columbia Univ., New York, NY

Abstract: SETD1A loss-of-function mutations confer large increases in schizophrenia (SCZ) risk. Our group previously characterized aspects of SETD1A+/- mice, recapitulating several key SCZ phenotypes, including lower dendritic spine density in anterior cingulate cortex, axon branching in somatosensory cortex (S1), and cognitive deficits. Decreased functional connectivity and altered network efficiency were reported in 3D cultures of neurospheres harvested from SETD1A+/- mice compared to wildtype (WT). We predicted that SETD1A deficiency impairs sensory-evoked activity within and intrinsic/resting-state functional connectivity (rsFC) between murine cortical brain regions. To test this we are using a new non-invasive in vivo imaging method known as widefield calcium imaging. All mice express GCaMP6 in neurons and GCaMP6 (ΔF/F) is the primary outcome measure. At interim analysis, data from n=5 female mice were analyzed (eventual n=10 mice/sex/genotype). Both sexes are included. Blue (470nm) and UV (395nm) LEDs are strobed sequentially at 40Hz to detect and separate calcium from non-calcium signals, respectively. The data are detrended, hemodynamics spatially regressed from calcium activity, transformed into ΔF/F and segmented into CCF brain regions. We simultaneously measure and score behavior using DeepLabCut and epoch the data based on behavior state. T-tests are used to evaluate group differences in evoked activity peaks and t-tests, correcting for multiple comparisons to evaluate differences in z-transformed Pearson's pairwise correlations for rsFC at the mouse level. Preliminarily, we find evidence of reduced maximum peak amplitude in SETD1A+/- mice compared to WT in left barrel cortex specifically ($t(48)=-3.57$, $p=0.00147$) during whisker stimulation. Reduced activity in left barrel cortex may be interpreted as a functional consequence of decreased axon branching in SETD1A+/- mice. A finding of decreased network connectivity between left and right barrel cortices would provide complementary evidence that SETD1A deficiency impairs sensory-evoked activity in and intrinsic/rsFC between murine cortical brain regions. Future directions include correlations between activity and connectivity perturbations with molecular and cytoarchitectural changes as well as pharmacological rescue assays. Patients with schizophrenia exhibit decreased sensory evoked potentials and altered rsFC. Our findings may reveal the neural substrates that underlie such intermediate phenotypes and cognitive impairments in schizophrenia, offering potential drug targets.

Disclosures: A. Doran: None. **E. Parker:** None. **D.S. Peterka:** None. **J.A. Gogos:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.01/Q5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Ultra-sensitive multiplex detection of mouse proinflammatory cytokines in mouse models of neurodegeneration using electrochemiluminescent (ECL) detection

Authors: L. DREBUSHENKO, A. SCHNEIDER, K. LEVER, D. BRISSETTE, ***J. RANDALL**, S. HARKINS, J. DEBAD, J. WOHLSTADTER;
MesoScale Diagnostics, LLC, Rockville, MD

Abstract: Neurodegeneration is a common feature in many central nervous system (CNS) conditions, including but not limited to Alzheimer's, Parkinson's, and Huntington's diseases, amyotrophic lateral sclerosis, multiple sclerosis, stroke, and traumatic brain and spinal cord injuries. Together, these conditions impact approximately 80-120 million people worldwide and represent the second leading cause of death around the world. Shared among these conditions is the progressive loss of CNS neurons, often with abnormal protein accumulation, and downstream inflammatory responses. The distinct inflammatory profile that accompanies each condition provides a non-invasive tool for obtaining disease state information for studying the progression of disease. To support our mechanistic understanding of these conditions, there remains a need for more efficient, higher sensitivity research tools that can spare valuable sample volume. This is of particular importance for multi-marker measurements as is the case for investigation of proinflammatory cytokines in neuroinflammation in mouse models. Here we describe an ultra-sensitive multiplex immunoassay panel that detects up to ten biomarkers in a single incubation step. This method further reduces the required volume of sample by increasing the sensitivity toward the ten markers of inflammation that were analyzed: IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, KC/GRO, IL-10, IL-12p70, and TNF-α. Distinct expression profiles of these cytokines are indicative of specific CNS disease states, progression, and severity. Using this ultra-sensitive platform, we show consistent detection of all ten markers from 1-2 µL of mouse serum and plasma from both control mice and murine models of neurodegeneration. Specifically, all ten analytes can be measured in mouse serum and plasma in the range of femtograms per milliliter.

Disclosures: L. Drebushenko: A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA. **A. Schneider:** A. Employment/Salary (full or part-time):; MesoScale Diagnostics, LLC. (MSD), Rockville, MD, USA. **K. Lever:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA. **D. Brissette:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA. **J. Randall:** A. Employment/Salary (full or part-time):; MesoScale Diagnostics, LLC. (MSD), Rockville, MD, USA. **S. Harkins:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA. **J. Debad:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA. **J. Wohlstadter:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. (MSD), Rockville, MD, USA.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.02/Q6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: JST SPRING, JPMJSP2119

Title: Differentiation potential of human bone marrow-derived mesenchymal stem cells cultured with laminin-511 E8 fragment

Authors: *H. WATANABE[1], M. NISHIURA[1], T. YAMAMOTO[2], T. IIMURA[1];
[1]Hokkaido Univ., Sapporo, Japan; [2]Matrixome Inc., Suita/ Osaka, Japan

Abstract: The control of fate and function of stem cells by manipulating the molecular composition of ECM is an attractive approach in regenerative medicine. Laminins (LMs) are major components of such ECMs, and are trimeric proteins of α, β, and γ chains, which comprise five α chains (α1, α2, α3, α4, and α5), three β chains (β1, β2, and β3) and three γ chains (γ1, γ2, and γ3), yielding 16 LM isoforms with distinct chain combinations. LM 511 (laminin isoform consisting of α5, β1 and γ1 chains) , the major component of the basement membrane underlying multipotent embryonic epiblasts, is suitable for maintaining undifferentiated human embryonic stem cells and iPSCs. Currently, active fragment of LM511 (LM511-E8) recombinantly produced have been used as a culture substrate for maintaining undifferentiated iPSCs. Mesenchymal stem cells (MSCs) exhibit diverse differentiating abilities. Bone marrow-derived MSCs (BMMCSs) are explored for treating bone regeneration. To obtain enough amount of MSCs for regenerative therapies, cell population is needed to be expanded in cell culture media with avoiding cellar senescence of MSCs tended to adipogenesis. Conventional cell culture media contain animal-derived serum (Xeno-media), which leads to concerns related to xenogenic response and animal-derived pathogens. To solve these concerns, Xeno-free culture media has been developed. However, it is still largely unknown whether Xeno-free media has equivalent effects as Xeno-media has on MSCs. This study compared the effects of a commercially available Xeno and a Xeno-free media with LM511-E8 on human BMMSCs. We first performed experiments using BMMSCs only on passage 2. BMMSCs cultured in the Xeno-free condition with LM511-E8 showed promoted osteogenic and suppressed adipogenic capacities compared to those in the Xeno condition. The Xeno-free group of cells exhibited homogenous cell morphology with fissional mitochondria, while the Xeno group of cells was morphologically heterogenous with fusional mitochondria. We further performed metabolome analysis using LC/MS-MS. After seven days culture, in Xeno-free media group, lysin and glutamate were significantly consumed, suggesting these metabolic changes reflecting the differentiation potential of BM-MSCs. Gene expression analysis by RT-qPCR of stemness, adipogenic, osteogenic and neurogenic differentiation markers supported these findings. Together, our findings suggested that the Xeno-free culture condition with LM511-E8 more effectively maintained favorable differentiation potentials of BMMSCs.

Disclosures: H. Watanabe: None. **M. Nishiura:** None. **T. yamamoto:** A. Employment/Salary (full or part-time):; Matrixome Inc.. **T. Iimura:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.03/R1

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH grant RF1MH132596-01

Title: Mapping neural connectivity at a single cell level using barcoded rabies virus and in situ sequencing

Authors: *S. KHEM[1], X. CHEN[1], M. RUE[1], A. ZHANG[1], I. R. WICKERSHAM[2], S. YAO[1]; [1]Allen Inst. for Brain Sci., Seattle, WA; [2]MIT, Cambridge, MA.

Abstract: Understanding the precise connection among diverse neurons is vital for unraveling brain structures and function. Despite considerable advances in technology, mapping single-cell synaptic connections at scale remains a formidable challenge. The current gold standard in mapping synaptic connectivity involves imaging using electron microscopy, but this approach is time consuming, labor intensive, and can only be applied to a small region. Furthermore, it is difficult to associate transcriptomic identities of neurons with connectivity. Alternatively, viral monosynaptic tracing can be used to map synaptic connectivity of a targeted neuronal population, but this method cannot resolve connectivity of single neurons. We propose to map synaptic connectivity and associate connectivity with transcriptomic identities of neurons at cellular resolution using barcoded rabies virus and in situ sequencing. In a pilot study, we showed that unambiguously resolving connectivity of single neurons requires maximizing the survival of source cells and minimizing interconnections among source cells. To achieve these goals, we refined viral strategies to optimize the number of source cells and to minimize cell death. Subsequently, we will apply this approach to map cell type-specific inputs to Cre-defined subpopulations of neurons and validate the results using previous monosynaptic tracing data with non-barcoded rabies virus. Our approach promises to transform the scale at which cell type-specific synaptic connectivity can be resolved.

Disclosures: S. Khem: A. Employment/Salary (full or part-time):; Allen Institute. **X. Chen:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **M. Rue:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **A. Zhang:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **I.R. Wickersham:** A. Employment/Salary (full or part-time):; MIT. **S. Yao:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.04/R2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R61/R33AT010408
NIH Grant R01NS105755-01A1
NIH Grant R01MH117293

Title: Microrna-mediated obstruction of stem-loop alternative splicing (mimosas): a novel mechanism for the regulation of alternative splicing in drosophila

Authors: *K. RUAN[1], R. G. ZHAI[2];
[1]Dept. of Neurol., Div. of Biol. Sci., The Univ. of Chicago, Chicago, IL; [2]Neurol., The Univ. of Chicago, Chicago, IL

Abstract: While RNA secondary structures are critical to regulate alternative splicing of long-range pre-mRNA, the factors that modulate RNA structure and interfere with the recognition of the splice sites are largely unknown. Previously, we identified a microRNA that regulates the outcomes of *Nmnat* pre-mRNA alternative splicing through the obstruction of stable stem structure formation. However, the fundamental question remains whether such microRNA-mediated interference with RNA secondary structures is a universal molecular mechanism for regulating mRNA splicing in *Drosophila*. Here, we introduce a bioinformatic pipeline to predict candidate microRNAs that potentially interfere with pre-mRNA stem-loop structures. To experimentally test predictions, we engineered a split fluorescence protein-based genetic splicing reporter system and demonstrated the computationally predicted effects of microRNAs in regulating long-range pre-mRNAs splicing *in vivo* in *Drosophila*. Specifically, we observed that microRNAs can either disrupt or stabilize stem-loop RNA secondary structures to influence splicing outcomes. Our study suggests that MicroRNA-Mediated Obstruction of Stem-loop Alternative Splicing (MIMOSAS) is a novel regulatory mechanism for the transcriptome-wide regulation of alternative splicing, which expands the repertoire of microRNA function and further indicates cellular complexity of post-transcriptional regulation.

Disclosures: K. Ruan: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A provisional patent has been filed related to this work, as detailed below. US Provisional Patent Application No.: 63/633,084, Title: MICRORNA-MEDIATED OBSTRUCTION OF STEM-LOOP ALTERNATIVE SPLICING. **R.G. Zhai:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A provisional patent has been filed related to this work, as detailed below. US Provisional Patent Application No.: 63/633,084, Title: MICRORNA-MEDIATED OBSTRUCTION OF STEM-LOOP ALTERNATIVE SPLICING..

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.05/R3

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NSF Grant 2109906

Title: Advancing tardigrades as an emerging model for systems-level neuroscience: Methods development in neuronal mapping and transgenics

Authors: *A. M. LYONS[1], M. GAME[2], F. SMITH[2], S. KATO[3];
[1]Neurol., Univ. of California, San Francisco, San Francisco, CA; [2]Biol., Univ. of North Florida, Jacksonville, FL; [3]Neurol., UCSF, San Francisco, CA

Abstract: The microscopic animals known as tardigrades, with their unique combination of morphological simplicity and behavioral complexity, present an untapped opportunity for advancing systems-level neuroscience. Tardigrades are composed of only a few thousand cells, yet exhibit a sophisticated array of motor behaviors despite their rudimentary nervous system, consisting of a multi-lobed brain, eyespots, a ventral nerve cord, paired ganglia, and limbs, among other structures. While some immunostaining of nervous system structures has been performed in this clade, almost no work has been performed to characterize neuronal identity and structure, connectivity, or record neural activity in this promising model organism. Here, we address these gaps by establishing tardigrades as a novel model for systems-level neuroscience research, leveraging tardigrades genetic simplicity, optical transparency, and the distinct advantages they offer for real-time visualization of neural processes. First, we create the most detailed neural mapping of a tardigrade species (*Hypsibius exemplaris*) to date, utilizing HCR *in situs* of pan-neuronal and neuron-specific transcripts. Second, we develop and refine transgenic techniques, specifically employing, extrachromosomal vector, transposon, and CRISPR-based methods, to introduce pan-neuronal GCaMP indicators (testing cargo delivery by microinjection, electroporation, transfection, and other experimental methods). In future work, these indicators will enable the visualization of neural activity in freely behaving transgenic tardigrades, providing insights into the neural basis of their complex behaviors and resilience. The integration of cutting-edge microscopy and genetic engineering techniques promises to unlock new avenues for research into neural function and resilience, positioning tardigrades as a pivotal model organism for both basic and translational neuroscience.

Disclosures: A.M. Lyons: None. **M. Game:** None. **F. Smith:** None. **S. Kato:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.06/R4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Characterization of Exosome Isolation and Lysis Methods from Human Plasma

Authors: *N. PROCTOR[1,2], R. VAN HORN[3,2], S. MCELYEA[3,2], T. A. DAY[1,2];
[1]Neurodegeneration, Eli Lilly and Co., Indianapolis, IN; [2]Eli Lilly and Company, Indianapolis, IN; [3]Autoimmune, Eli Lilly and Co., Indianapolis, IN

Abstract: Background There is increasing interest to utilize extracellular vesicles (EVs) as a source of protein biomarkers. For neurodegenerative diseases, including Alzheimer's disease (AD), exosomes are a potential source for spreading pathological proteins such as β-amyloid, tau, and α-synuclein in the brain. All mammalian cells release and take up EVs in a range of sizes, including exosomes, which are small, lipid-bilayer enclosed nanoparticles (30-100 nm in diameter) containing proteins, RNA, and other cellular components, that are involved in intercellular communication. There is vast heterogeneity in the isolation and analytical techniques used to characterize exosomes and their cargoes, and methods intended to interrogate biomarkers within the luminal compartment of exosomes often lack confirmation that vesicle lysis has occurred. Much of the difficulty with exosome isolation from human biofluids has been in the identification of reproducible enrichment techniques and the ability to measure intraluminal biomarkers, especially proteins in low abundance.
MethodsThe aim of this study was to identify a robust isolation technique for the enrichment of extracellular vesicles from human biofluids, such as plasma, and determine the optimal yield of exosomes using nanoparticle tracking analysis (NTA), such as particle count, diameter, and positive and negative exosomal markers. Exosomes were then treated with various lysis techniques, including triton X-100, chloroform, and cyclohexane, and the efficiency of the lysis was measured by NTA and identification of intraluminal biomarkers, such as tau.
ResultsTo minimally exclude non-exosomal populations, size exclusion chromatography was the preferred method of EV isolation. Utilizing organic solvent was the fastest method for lysis of EVs but resulted in potential protein aggregation. Detergents, such as sodium dodecyl sulfate, Triton X-100, and Tween 20, were also able to lyse the EVs in a time-dependent manner. To achieve a relatively rapid lysis, heating of the sample with detergent was required to achieve >90% reduction in particle count. Upon EV lysis, changes in the levels of specific tau species were detected, suggesting their presence in the luminal compartment.
ConclusionThese data demonstrate optimal techniques for enriching exosomes from human biofluids, such as plasma, and measuring intraluminal protein cargoes serving as AD biomarkers.

Disclosures: N. Proctor: A. Employment/Salary (full or part-time):; Eli Lilly and Company. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly and Company. **R. Van Horn:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **S. McElyea:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **T.A. Day:** A. Employment/Salary (full or part-time):; Eli Lilly and Company.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.07/R5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: CIHR grant

Title: Optimization of a protocol to extract and sequence human cortical neurons surrounded by a perineuronal net

Authors: *D. J. LUMLEY[1,2], C. BELLIVEAU[3], N. MECHAWAR[4];
[1]Integrated Program of Neurosci., McGill, Sherbrooke, QC, Canada; [2]Douglas Institute, Montreal, QC, Canada; [3]Douglas Hosp. Res. Ctr., Montreal, QC, Canada; [4]Douglas Inst., Montreal, QC, Canada

Abstract: Introduction: Interest in perineuronal nets (PNNs) has grown steadily, namely in the fields of neurodegeneration, memory, and early-life adversity. Despite this, the transcriptomic profile of neurons encapsulated by these structures have yet to be characterized. We recently decided to develop a protocol that would allow us to address this question in human post-mortem cerebral cortex, with the aim of using this approach to study samples from psychiatric subjects. As PNNs are extracellular, existing cell sorting technologies are not a viable option, and we thus opted to use laser capture microdissection (LCM). LCM provides an opportunity to collect homogenous samples in an accurate and contactless manner. **Methods:** Frozen post-mortem samples of ventromedial cortex (vmPFC) from four individuals (3 males, 1 female, aged 54-72) were provided by the Douglas-Bell Canada Brain Bank. Tissues were cut with a cryostat into 10µm-thick sections and underwent different fixation protocols and stains, immediately prior to LCM extraction. Following LCM extraction, samples are purified using the PicoPure^{TM} RNA isolation kit (Thermo Fischer Scientific). cDNA synthesis is carried out using the Smart-Seq mRNA LP kit (Takara Bio). cDNA quality is evaluated with qPCR, and samples are probed for two separate housekeeping genes (β;;;-actin and GAPDH) to assess purity. **Results:** After multiple rounds of optimization, our current protocol seems compatible with library preparation. Indeed, we have managed to generate sufficiently high-quality cDNA, in concentrations on-par with our positive control, which tests positive for both housekeeping genes, indicating very low genomic contamination. The ongoing optimization should be completed shortly and the protocol presented in full at the meeting. **Conclusion:** With this approach, we are hopeful that we will be able to examine the first transcriptomic profiles of PNN-encapsulated neurons. To our knowledge, this has yet to be accomplished in any species. The next step will be to apply this protocol to compare PNN-embedded neurons in vmPFC samples from depressed suicides vs matched controls.

Disclosures: D.J. Lumley: A. Employment/Salary (full or part-time):; McGill University Integrated Program of Neuroscience, Douglas Research Center. **C. Belliveau:** A. Employment/Salary (full or part-time):; Douglas Research Center, McGill University Integrated Program of Neuroscience. **N. Mechawar:** A. Employment/Salary (full or part-time):; Douglas Research Center, McGill University Integrated Program of Neuroscience, McGill University Department of Psychiatry.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.08/R6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: JST SPRING, JPMJSP2119

Title: Laminin 511-E8 stimulated the differentiation PC12 cells into catecholaminergic neurons

Authors: *M. NISHIURA[1], H. WATANABE[1], T. YAMAMOTO[2], T. IIMURA[1];
[1]Pharmacol., Hokkaido Univ., Sapporo, Hokkaido, Japan; [2]Matrixome Inc., Suita/ Osaka, Japan

Abstract: Through interactions with their surrounding extracellular matrix (ECM), cells regulate their activities such as proliferation, differentiation, and cell death in conjunction with the signals elicited by a variety of growth factor receptors. The control of fate and function of stem cells by manipulating the molecular composition of ECM is an attractive approach in regenerative medicine. Laminins (LMs) are major components of such ECMs, and are trimeric proteins of α, β, and γ chains, which comprise five α chains (α1, α2, α3, α4, and α5), three β chains (β1, β2, and β3) and three γ chains (γ1, γ2, and γ3), yielding 16 LM isoforms with distinct chain combinations. LM511 (laminin isoform consisting of α5, β1 and γ1 chains), the major component of the basement membrane underlying multipotent embryonic epiblasts, is suitable for maintaining undifferentiated human embryonic stem cells and iPSCs. Currently, active fragment of LM511 (LM511-E8) recombinantly produced have been used as a culture substrate for maintaining undifferentiated iPSCs. The LM511-E8 also supports the induction of neural differentiation of iPSCs, potentiating the cell replacement therapy of Parkinson's disease. Rat pheochromocytoma cells PC12 have extensively used in neurobiology, since they morphologically and functionally differentiate into sympathetic ganglion neurons in the presence of nerve growth factor (NGF). PC12 cells also widely used as models for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. To investigate how distinct LM isoforms affect neuronal cell survival and differentiation, we cultured PC12 cells either on iMatrix-511 (recombinant LM511-E8) or iMatrix-221 (recombinant LM221-E8). Changes in cytoskeletal structure and gene expressions were assessed. The iMatrix-511 and iMatrix-221 coating treatments decreased the expression of the neurotrophins like *Ngf*, *Bdnf*, and *Ntf3* and the undifferentiated marker *Sox2*. Furthermore, iMatrix-511 increased the expression of *TH* encoding tyrosine hydroxylase and *VIP* encoding vasoactive intestinal peptide, while iMatrix-221 showed no significant differences in these transcripts. Immunocytochemical observations showed that the cell bodies were obviously large and round-shaped in the iMatrix-511 groups while the cell bodies were small and square-shaped in the control and iMatrix-221 groups. These results revealed that the LM511-E8 specifically stimulated the differentiation PC12 cells into catecholaminergic neurons. This suggests the possibility of inducing specific functional neurons by manipulating the compositions of ECM.

Disclosures: M. Nishiura: None. **H. Watanabe:** None. **T. yamamoto:** A. Employment/Salary (full or part-time):; Matrixome Inc.. **T. Iimura:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.09/S1

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Development of real time and high throughput detection technology for nicotine metabolites and neurotransmitters based on microfluidics

Authors: L. CUI, M. ZHU, ***H. HOU**;
Beijing Life Sci. Acad., Beijing, China

Abstract: Nicotine exhibits protective properties against a number of neurodegenerative illnesses due to its ability to quickly cross the blood-brain barrier and trigger chemical interactions with neurotransmitters. Consequently, nicotine has emerged as a promising therapeutic agent for the treatment of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). However, the mechanism by which nicotine and its metabolites regulate neurotransmitter changes remains unclear. Additionally, the current research methods have limitations in terms of detection sensitivity, temporal resolution, and spatial resolution, which hinder the investigation into the mechanisms by which nicotine and its metabolites regulate neurotransmitters. The microfluidic chip reduces the need for manual sample preparation and enhances experimental throughput by enabling online automatic derivatization. This study developed a real-time, high-throughput online detection approach for monitoring the levels of neurotransmitters and nicotine metabolites in rat cerebral fluid. We achieved this by integrating the in vivo microdialysis sampling methodology, microdialysis online derivatization, and HPLC-MS/MS. With a brief sample collection time and a 1 μL injection volume, the approach successfully separates target chemicals in 10 minutes. It has a good linear range ($R^2 > 0.99$) and quantification limits were 0.004 ~ 5.52 ng/mL, along with detection limits were 0.001 ~ 160 ng/mL. The establishment of this method offers a deeper comprehension of the dynamic concentration variations between neurotransmitters and nicotine. It is crucial to comprehend the biological effects of nicotine as well as the mechanisms underlying its effects on neurotransmitters.

Disclosures: L. Cui: None. **M. Zhu:** None. **H. Hou:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.10/S2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Quantifying dopamine D2 and adenosine A2A receptor interactions in rat brain using MolBoolean™ technology

Authors: M. MALMQVIST, A. CHARBONNEAU, C. MARKS, ***E. KUTEEVA**;
Res. and Develop., Atlas Antibodies, Bromma, Sweden

Abstract: Investigating protein-protein interactions (PPIs) is crucial for understanding normal neuronal functions and dysregulation in neurological disorders. We utilized MolBoolean™, a newly developed *in situ* proximity assay, to simultaneously detect free and interacting protein fractions of the dopamine D2 (DRD2) and adenosine A2A (ADORA2A) receptors in rat brain sections.
MolBoolean™ employs anti-mouse and anti-rabbit secondary proximity probes with an oligonucleotide setup enabling the detection of free and interacting proteins within ~40 nm of proximity using immunofluorescent detection reporters (ATTO565 and ATTO647N). In the present study, MolBoolean™ was used to assess the PPI between DRD2 and ADORA2A receptors in formalin-fixed paraffin-embedded brain sections of adult rats (n=3), using anti-DRD2 (HPA015139) and anti-ADORA2A (Ab 05-717) antibodies. Simultaneous immunofluorescent IHC (IHC-IF) analysis with anti-GAD1 (AMAb91079) and anti-GFAP antibodies (AMAb91033) enabled the evaluation of MolBoolean results specifically in neurons and astrocytes.
Both IHC-IF and MolBoolean revealed high expression of DRD2 and ADORA2A receptors in the rat striatum and low expression in the rat cerebral cortex. A relatively high percentage of receptor expression was seen in neurons, while astrocytes exhibited a relatively low percentage of receptor expression levels. MolBoolean analysis indicated that approximately 20% of DRD2 and ADORA2A receptors were interacting in both neuronal spines and astrocytes in the striatum, while approximately 55% and 25% of ADORA2 and DRD2, respectively, were present as free proteins. Strikingly, cortical DRD2-ADORA2A interactions were only 2.5%, markedly lower than in the striatum. These results were consistent when analyzing the total number of DRD2 and ADORA2 receptors present in heterodimer complexes. A relatively high percentage of total DRD2 in complex with ADORA2 was evident in the striatum, and the reverse was observed in the cortex.
These results demonstrate the successful use of MolBoolean technology in detecting individual and interacting ADORA2 and DRD2 proteins in rat brains. Moreover, the combination of MolBoolean with IHC-IF enabled PPI quantification in distinct cell subpopulations. MolBoolean™ can be used as a powerful tool for dissecting PPIs underlying normal brain functions and their dysregulation in neurological disorders.

Disclosures: M. Malmqvist: A. Employment/Salary (full or part-time):; Atlas Antibodies. **A. Charbonneau:** A. Employment/Salary (full or part-time):; Atlas Antibodies. **C. Marks:** A. Employment/Salary (full or part-time):; Atlas Antibodies. **E. Kuteeva:** A. Employment/Salary (full or part-time):; Atlas Antibodies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atlas Antibodies.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.11/S3

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Comprehensive pharmacological profiling of the human 5-HT_{7a} receptor isoform exposes novel signaling

Authors: C. NORMAND[1], **G. DUGAST**[1], L. SABBAGH[1], T. RAY[2], P. WREN[2], *A. MANCINI[1];
[1]Domain Therapeut. NA Inc., Saint-Laurent, QC, Canada; [2]Mindstate Design Labs, South San Francisco, CA

Abstract: The 5-HT (serotonin) receptor type 7 (5-HT_7R) is one of the most recently identified members of the 5-HT receptor family. Pharmacological modulation of this G protein coupled receptor (GPCR) is considered a promising approach for the treatment of various neurological and psychiatric disorders including anxiety, depression, schizophrenia and Alzheimer's disease[1]. Human (h)5-HT_7R has been reported to couple primarily to Gαs[2,3], which activates adenylate cyclases and leads to the production of cAMP. However, it has now become evident that many GPCRs can couple to more than one signaling pathway, and that different ligands acting at a given receptor can selectively promote the activation of different subsets of these pathways. This so-called "functional selectivity" (or biased signaling) highlights the importance of exhaustively testing multiple ligands on multiple signaling pathways when defining a receptor's signaling repertoire.
To date, h5-HT_7R's full signaling signature in response to different ligands remains unexplored. In this work, we applied our bioSens-All® platform of enhanced bystander BRET-based biosensors to profile the signaling and pharmacology of ten diverse 5-HT_7R ligands (5-HT, 5-CT, 8-OH DPAT, AS-19, LP-44, LP-211, Serodolin, SB-269970, Methiothepin and LSD) at the recombinantly expressed h5-HT_{7a}R isoform in HEK293 cells. The agonist and antagonist activity of each ligand was characterized on an extensive panel of sixteen pathway-specific biosensors. The results obtained confirmed h5-HT_{7a}R's coupling to Gαs, but also exposed novel couplings to brain-enriched Gi/o-family G proteins (i.e., GαoA, GαoB, Gαz), Gα13 and (especially) Gα15. Interestingly, comparison of the ligand activity on Gαs and the newly identified Gα15 pathway enabled the broad classification of compounds into five functionally distinct pharmacological clusters. Among the identified clusters, one defined by LP-44 and LSD for example produced a switch in h5-HT_{7a}R G protein coupling. Specifically, ligands in this cluster displayed no detectable agonist activity on Gαs; instead, they fully antagonized 5-HT-induced Gαs signaling while showing agonist activity on Gα15 and other pathways.
These data shed new light on h5-HT_{7a}R pharmacology and may help inform and expand the therapeutic exploitation of this receptor in various CNS indications as different chemotypes may induce differential functional selectivity.
References:1. Fukuyama *et al*. Int J Mol Sci. 2023 Jan 20;24(3):2070. 2. Guseva *et al*. Front Behav Neurosci. 2014 Oct 1:8:306. 3. Krobert *et al*. Naunyn Schmiedebergs Arch Pharmacol. 2001 Jun;363(6):620-32.

Disclosures: C. Normand: A. Employment/Salary (full or part-time):; Domain Therapeutics NA Inc. **G. Dugast:** A. Employment/Salary (full or part-time):; Domain Therapeutics NA Inc. **L. Sabbagh:** A. Employment/Salary (full or part-time):; Domain Therapeutics NA Inc. **T. Ray:** A. Employment/Salary (full or part-time):; Mindstate Design Labs. **P. Wren:** A. Employment/Salary (full or part-time):; Mindstate Design Labs. **A. Mancini:** A. Employment/Salary (full or part-time):; Domain Therapeutics NA Inc..

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.12/S4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIGMS P20GM109091-10S3

Title: The changes in viscoelastic properties of cytoplasm during stress granule formation

Authors: *E. KORUNOVA[1], V. SIKIRZHYTSKI[2], P. VASQUEZ[2], M. WYATT[2], M. SHTUTMAN[3];
[1]Univ. of South Carolina, COLUMBIA, SC; [3]Drug Discovery and Biomed. Sci., [2]Univ. of South Carolina, Columbia, SC

Abstract: Stress granules (SGs) are dynamic, non-membrane-bound cytoplasmic assemblies of RNA and proteins that form in the cytoplasm of cells in response to various stressors, including oxidative stress, heat shock, and viral infections. SGs are thought to protect cells from stress by sequestering and stabilizing unnecessary mRNAs and proteins during the stress response. However, chronic stress or mutations in SG components can lead to SG dysfunction, which can contribute to the pathogenesis of neurodegenerative diseases like Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis. SGs are defined by core protein markers, including G3BP1 and G3BP2; however, the SGs formed in different conditions may have different physical (or, more precise viscoelastic) properties that, in turn, define the functions of the SGs. Viscoelasticity, the key property of living systems, refers to a material's ability to both dissipate (viscous) and store (elastic) energy. Here, we aimed to determine the viscoelastic properties of SGs. Modified genetically encoded multimeric (GEM) nanoparticles were employed to determine the SGs' viscosity, and Saphire fluorescent protein was replaced for photo-activatable PA-GFP. The modification greatly improved the traceability of the particles in the subcellular locations. We analyzed the diffusion coefficient of SGs and the cytoplasm with the particles, using the mCherry-GBP1 as an SGs marker. Further, we developed a mathematical model that connected the parameters of SGs formation with the viscoelastic properties of cytoplasm. The approach will be applied to determine the physical properties of physiological and pathological SGs.

Disclosures: E. Korunova: None. **V. Sikirzhytski:** None. **P. Vasquez:** None. **M. Wyatt:** None. **M. Shtutman:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.13/S5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Novel RavZ-based probes and deconjugase for monitoring and studying mATG8-positive autophagic membrane in post-mitotic neurons

Authors: *H. CHOI[1], S.-W. PARK[2], D.-J. JANG[3], J.-A. LEE[1];
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Abstract: Autophagy is a cellular degradative pathway important for development and for maintenance of cellular homeostasis. Mammals ATG8s are play an essential role in autophagy pathway, including autophagosome formation, cargo selection and recruitment of proteins bearing LC3-interacting region (LIR) motifs. While overexpression of green fluorescent protein(GFP) fused LC3/GABARAP systems are common for monitoring autophagy. However, overexpression of LC3/GABARAP proteins has been reported to hyperactivate basal autophagy levels, while also leading to self-aggregation issues caused by GFP protein. RavZ is a protein secreted by *Legionella* that irreversibly delipidates mammalian mATG8 on autophagic membranes. Previously, we identified specific LIR motifs for each LC3/GABARAP. Using these selective LIR motifs, we generated RavZ based novel autophagosome monitoring probes. In this study, we evaluated the effect of our new probe on autophagy activity compared to the conventional overexpression of GFP-LC3/GABARAP. This probe efficiently localized to LC3/GABARAP-positive autophagosomes without affecting autophagy activity. Furthermore, we evaluated autophagy flux using the GFP-RFP fused tandem-probe. We also generated LC3A/B-PE selective deconjugase based on RavZ protein. By modifying LIR motifs at the deconjugase's terminals, we significantly influenced its selectivity toward LC3A/B. Additionally, modifying the α3 helix to decrease hydrophobicity and reduce membrane residence time enhanced this specificity. We propose that these new RavZ based probes and deconjugase will be useful for monitoring and studying the function of mATG8-positive autophagic membranes in autophagy research.

Disclosures: H. Choi: None. **S. Park:** None. **D. Jang:** None. **J. Lee:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.14/S6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NCMH Grant of Korea RS-2024-00413115
NIH award 5R01NS112176-04
NIH award 1R42NS125895-01A1
NIH award 1R01NS129549-01

Title: Anti-immune electrodes for long-term monitoring of neurotransmitter concentration

Authors: *Y. KWAK[1,3,4], H. CHO[1], J. JANG[2], Y. OH[5,3,4], H. SHIN[5,3,4], K. H. LEE[5,4], D. JANG[1,2];
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Abstract: Tonic neurotransmitter concentration serve as critical biomarkers for diagnosing depression, chronic stress, and addiction. Various studies aim for measuring neurotransmitter over a long-term period, however, there has been a limitation in acquiring stable signals due to the interference caused by the immune response occurring around the implanted electrodes. In this study, we employed red blood cell membrane (RBCM)-coated carbon fiber microelectrode (CFM) and reference electrode (REF) to prevent immune responses and confirmed the ability to measure tonic dopamine concentrations over long period. The coating on the electrode surface was validated with scanning emission microscopy (SEM), energy dispersive spectroscopy (EDS) and confocal image which were consistent with the reference paper. The electrochemical characteristics of the RBCM-coated electrodes were verified by the open circuit potential (OCP) and electrochemical impedance spectroscopy (EIS). Furthermore, we tested the sensitivity to dopamine 1uM in an in-vitro environment and found no significant difference before and after coating. Finally, we confirmed the possibility of anti-fouling effect, by observing the phasic dopamine signals before/after bovine serum albumin (BSA) treatment. These findings prove that it is possible to measure stable tonic dopamine levels over the long term through biocompatible coated electrodes. In the future, we will apply this technology to brain disease models to elucidate the trends of tonic dopamine concentrations according to each disease.

Disclosures: Y. Kwak: None. **H. Cho:** None. **J. Jang:** None. **Y. Oh:** None. **H. Shin:** None. **K.H. Lee:** None. **D. Jang:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.15/T1

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: The Brain and Behavior Research Foundation NARSAD Young Investigator Award
Mary E. Groff Foundation
Trinity University Murchison
Department of Biology and Neuroscience Program funds

Title: Designing novel proteins to identify and decouple synaptically-connected neurons

Authors: A. FLANAGAN[1], G. Z. SUN[1], A. DANG[2], M. HORN[2], J. CLARK[3], E. FARRELL[2], C. WILLIAMS[4], J. VALADEZ[5], *G. M. J. BEAUDOIN, III[1];
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Abstract: While knowledge of the interconnected brain areas can identify information flow in the brain, an understanding of the microcircuit between these areas is required to understand the logic behind the modification of this information from brain region to brain region. We are using a synthetic biology approach to create two new tools for identifying and modifying the microcircuit. These tools are unique from previous tools by relying on protein components interacting across a synapse to activate the signaling.
For trans-synaptic labeling, we are co-opting the C. elegans orthologs for the Notch-Delta signaling system, Glp-1 and Lag-2, respectively. Glp-1 was modified by replacing the intracellular portion of the protein with cre-recombinase, a site directed DNA recombination enzyme. We hypothesize that cells expressing the chimeric Glp1-Cre protein will be activated by coming in contact with a cell expressing Lag-2, thereby releasing cre-recombinase to induce expression of a fluorescent protein. This system has successfully led to recombination in cultured non-neuronal cells, including expression of cre-dependent fluorescent molecules and release of cre recombinase.
To modify synapses, we are developing a chimeric protein, CadPlexin, to induce selective loss of synapses. CadPlexin is composed of the extracellular domain of D. melanogaster DE-Cadherin and the transmembrane and intracellular domain of M. musculus Plexin-B2. Cadherins bind to one another homophillically, acting to bind cells with one another. Plexins, when dimerized and activated by their usual ligand, Semaphorin, will cause a downstream signaling cascade that induces cell-cell repulsion. We hypothesize that, when two cells expressing CadPlexin are in close contact (i.e. at a synapse), CadPlexin will selectively destroy the synapse, as the extracellular domains from DE-Cadherin will bind together and mimic semaphorin binding and clustering required to activate plexin signaling. Using non-neuronal cells, we find that CadPlexin expression leads to isolation and avoidance of cells. Additionally, activation of CadPlexin signaling through antibody clustering induces actin polymerization consistent with stress fibers and not lamellipodia.
Future work is directed towards testing these constructs in primary culture neurons. Together, these tools will allow us to label synaptically connected neurons and destroy synapses with surgical precision by targeting synapses between some neurons while leaving synapses with nearby neurons of a different type intact.

Disclosures: A. Flanagan: None. **G.Z. Sun:** None. **A. Dang:** None. **M. Horn:** None. **J. Clark:** None. **E. Farrell:** None. **C. Williams:** None. **J. Valadez:** None. **G.M.J. Beaudoin:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.16/T2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: R01DC017303 (NC)
R01DC018733 (NC)
Buoniconti Fund

Title: An enhanced transsynaptic labeling system optimized for peripheral sensory neurons

Authors: G. DVORYANCHIKOV[1], B. C. CAMPBELL[2], P. TSOULFAS[3], ***N. CHAUDHARI**[4];
[1]Physiol. and Biophysics, Univ. of Miami Miller Sch. of Med., Miami, FL; [2]Neurosciences, UC San Diego, La Jolla, CA; [3]Neurosurg. and The Miami Project, Univ. of Miami, Miami, FL; [4]Univ. of Miami Sch. of Med., Miami, FL

Abstract: There are few transsynaptic tracing studies that have mapped neuronal connectivity from peripheral sensory afferents into the brain. Pseudorabies, Adeno Associated Virus (AAV), and VSV are important tools for transynaptic mapping across diverse brain regions. However, these methods entail stereotaxic injection of the virus at anatomically precise sites. This requirement is not well suited to the distributed receptive field of many afferents including those of the somatosensory, vagal, and gustatory systems. Wheat germ agglutinin (WGA), fused with mCherry (mWmC) was recently shown to be transsynaptically transported (Tsai et al, 2022). We addressed the challenge posed by the distributed receptive field of peripheral sensory afferents by delivering mWmC using a synthetic serotype, AAV-PHP.S, known to efficiently transduce peripheral sensory ganglia. We injected AAV-PHP.S_*flex*-mWmC intravenously into Pirt-Cre mice (in which all sensory ganglion neurons express Cre). mWmC was readily detected within 2 weeks post-injection and accumulated further for at least 3 more weeks in many neurons of DRG, trigeminal, vagal and geniculate ganglia. mWmC was transported to the central terminals of each of these neuron types. In their postsynaptic target neurons, mWmC, taken up into the lysosomal compartment, appears punctate. To enhance the retention and brightness of the postsynaptic signal, we have also produced fusions of WGA with several additional fluorescent proteins, selected for brighter intrinsic fluorescence and stability at low pH. When transfected into cultured cells, one of these new constructs produces much brighter and larger puncta after uptake. *In vivo* as well, the neuronal label can be detected without the need for antibody amplification (whereas mWmC does require it). This permits greater flexibility for multiplexing with cell type markers and for imaging the postsynaptic neurons at higher resolution. DRG, trigeminal, vagal and geniculate ganglia have all been subjected to single-cell sequencing and their neurons classified transcriptionally. We are now in the process of using this optimized transsynaptic labeling method to draw 1-to-1 connections between specific subtypes of peripheral sensory afferents and their select central targets.

Disclosures: G. Dvoryanchikov: None. **B.C. Campbell:** None. **P. Tsoulfas:** None. **N. Chaudhari:** F. Consulting Fees (e.g., advisory boards); The Coca-Cola Company Scientific Advisory Board.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.17/T3

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Bridging the Gap in Synaptic Research: Visualizing Neurexin and Neuroligin Interactions Using Multiomic RNAscope Technology

Authors: G.-A. A. KIM[1], S. ZHOU[1], J. A. YU[1], Y. WANG[1], D. WAKHLOO[1], H. A. SEPASIZANGABADI[1], A. DIKSHIT[2], ***S. A. DESHPANDE**[1], L.-C. WANG[1], M. SRINIVASAN[1];
[1]Bio-techne, Newark, CA; [2]Advanced Cell Diagnostics, Newark, CA

Abstract: Synaptogenesis is a fundamental process of synapse formation that occurs during early development. The formation and regulation of synapses are crucial for all brain functions as they establish connections between neurons. Synaptic disruptions have been implicated in various neurological disorders, such as Alzheimer's, Parkinson's, and Frontotemporal Dementia. Proteins, both on the presynaptic and postsynaptic terminals, play an essential role in the formation of synapses. Neurexins (NRXs) and Neuroligins (NLGNs) are key protein players in synapse formation and maintenance. NRXs, as presynaptic cell adhesion molecules, are involved in the synaptic specification and differentiation of excitatory and inhibitory synapses. NLGNs, as postsynaptic proteins, regulate synaptogenesis and maintain synaptic stability. During development, neuroligins contribute to the fine-tuning of neural circuits. Mutations and deletions in the neurexin or the neuroligin genes have been linked to psychiatric disorders like autism, epilepsy, schizophrenia, and neurodegenerative disorders. The interaction between neurexins and neuroligins in the synaptic cleft is responsible for effective synaptic transmission and plasticity in learning and memory.
Understanding this interaction would lead to better disease modeling and identifying potential therapeutic targets for pharmacological interventions. However, current methods lack the ability to detect ligand/receptor protein-protein interactions (PPIs) with high specificity and sensitivity. To address this need, we developed a novel assay that modifies the existing RNAscopeTM technology to visualize PPIs, proteins, and mRNA in situ on the same tissue section. Protein targets were visualized in situ along with PPIs/mRNAs using an automated workflow on a Leica BOND Rx instrument. The assay can interrogate up to 1 PPIs and any combination of mRNA and/or protein targets. Here, we demonstrate the ability of this assay to detect and spatially visualize the interaction of the NRX/NGLN protein complex located at the presynaptic and postsynaptic terminals. The NRX/NGLN protein complex is known to regulate these terminals; we used RNA probes targeting excitatory presynaptic (Vglut1), inhibitory presynaptic (Vgat1),

and postsynaptic (Gabra1) terminals along with cell profiling antibodies NEUN and GFAP. The ability to detect and visualize protein-protein interactions with other mRNA molecules in the same tissue section offers a valuable tool for multi-omics analysis and accurate study of complex brain processes such as synaptogenesis in development, learning, memory, and disease.

Disclosures: G.A. Kim: None. **S. Zhou:** None. **J.A. Yu:** None. **Y. Wang:** None. **D. Wakhloo:** None. **H.A. Sepasizangabadi:** None. **A. Dikshit:** None. **S.A. Deshpande:** None. **L. Wang:** None. **M. Srinivasan:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.18/T4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Next-generation HCR™ RNA-FISH enables protease-free, scalable co-detection of RNA and protein in any sample

Authors: *A. L. MADDOX[1], C. SINGH[2], A. ARCHARYA[3];
[1]Mol. Instruments, Inc., Los Angeles, CA; [2]Support, Mol. Instruments, Alhambra, CA; [3]Mol. Instruments, Los Angeles, CA

Abstract: HCR™ RNA-FISH has become a cornerstone tool for visualizing RNA expression within intact sample types, ranging from cells in suspension, to tissue on slides, to whole-mount vertebrate embryos. Today, these kits utilize the HCR v3.0 architecture first developed in 2018, which itself enabled robust, turnkey RNA-FISH due to its innovative automatic background suppression implemented at a platform level, regardless of target or sample type. Molecular Instruments® (MI) supports thousands of users within neuroscience research community, working with over 500 unique species. Here, we demonstrate our latest innovation: the next-generation HCR™ v4.0 platform. Representing nearly ten years of engineering efforts, HCR™ v4.0 will drive cutting-edge biology research for the next decade by maintaining an enzyme-free approach, ensuring compatibility with any sample type, and significantly enhancing the performance of HCR™ assays by an order of magnitude.

Disclosures: A.L. Maddox: None. **C. Singh:** None. **A. Archarya:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.19/T5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Molecular Instruments®

Title: Parallel 10-Plex Imaging of RNA and Protein Targets with HCR™ RNA-FISH

Authors: C. SINGH[1,2], A. MADDOX[3], A. ARCHARYA[4];
[1]Support, Mol. Instruments, Los Angeles, CA; [2]Molecular Instruments, Los Angeles, CA; [3]Mol. Instruments, Inc., Los Angeles, CA; [4]Mol. Instruments, Los Angeles, CA

Abstract: HCR™ RNA-FISH serves as a fundamental tool for neuroscientists, empowering researchers with high performance, multiplex, quantitative imaging of RNA expression in any sample type, including highly autofluorescent whole-mount embryos, thick brain sections and FFPE tissue sections. The ability to map spatial organization of RNA and protein molecules within the same sample is critical for advancing our understanding of the complexity of the brain, thus providing deeper insights into neurodevelopmental and neurological disorders.Molecular Instruments® (MI) supports a vast community of neuroscientists worldwide, engaged in studying over 500 diverse species. MI is excited to announce the immediate availability of ready-to-use up to 10-plex assays that can be seamlessly adaptable to any sample type of interest to the scientist. Additionally, we also present an affordable, scalable, and automated platform capable of performing HCR™ assays to streamline high-throughput workflows.

Disclosures: C. Singh: None. **A. Maddox:** None. **A. Archarya:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.20/T6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIDA Grant R21DA052101

Title: Casmini toolkit for cell-type specific and light-inducible epigenome editing applications

Authors: *M. GREEN[1], S. GANAPATHY-KANNIAPPAN[2], R. CHANDRA[3], N. HAJIRNIS[4], E. CHOI[2], M. LOBO[5];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Univ. of Maryland, Baltimore, Baltimore, MD; [4]Anat. and Neurobio., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [5]Anat. and Neurobio., Univ. of Maryland SOM, Baltimore, MD

Abstract: CRISPR epigenome editing, using CRISPR-activation or CRISPR-interference (CRISPRa/i) allows for more physiologically relevant manipulation of gene expression. Previously, our lab has used Cas9 derived CRISPRa/i epigenome editing tools in Neuro2A cells

to manipulate a transcriptional program that was altered in specific neuronal populations in the brain following exposure to an addictive substance. Recent advances in CRISPR have paved the way for using a Cas12f derived system (CasMINI) instead of Cas9. The advantages of this system are twofold - First, dead (d)CasMINI is less than half the size of dCas9 allowing for packaging in adeno-associated viruses (AAVs) instead of the previously used lentiviruses. Further, this smaller construct allows the possibility of including multiple guide constructs for manipulation of multiple genes at the same time. We are utilizing a CRISPRi system in which a KRAB domain is fused to dCasMINI, and a CRISPRa system in which VP64 is fused to dCasMINI. These constructs are paired with a dCasMINI-compatible guide RNA (gRNA) construct. With this system, we target hub genes previously found to be upregulated and downregulated in significant gene network modules in mouse brain neuron stubtypes following forced abstinence from fentanyl. We have validated for the first time in Neuro2a cells that the dCasMINI fusion genes can express at the mRNA and protein level. We have also shown that both the dCasMINI-KRAB & dCasMINI-VP64 constructs paired with gRNA can successfully downregulate and upregulate targeted gene expression levels, respectively. We also have developed a light-inducible Opto-dCasMINI system for temporal-specific control of gene expression. For this platform, dCasMINI is fused to CIBN and KRAB or VP64 are fused to Cry2. Prior to light stimulation, the gRNA construct recruits dCasMINI-CIBN to the targeted gene locus and upon light stimulation, CIBN & Cry2 fuse, recruiting transcriptional regulator (VP64 or KRAB) to the promoter region of the target gene. We have successfully manipulated expression of target genes in-vitro using these tools. The potential to use these tools to alter transcription of specific gene(s) in a cell type-specific manner in the brain will allow routine use of AAV CRISPR epigenome editing tools in vivo.

Disclosures: M. Green: None. **S. Ganapathy-Kanniappan:** None. **R. Chandra:** None. **N. Hajirnis:** None. **E. Choi:** None. **M. Lobo:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.21/T8

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R01DA51100

Title: High-precision in-vivo Detection of Intracranial Procaine in Hippocampus and Lateral Ventricle of Freely Moving Rats

Authors: *K. WANG[1], K. HONEYWELL[2], N. A. EMMONS[3], T. E. KIPPIN[4];
[1]Univ. of California Santa Barbara Neurosci., Santa Barbara, CA; [2]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [3]Psychology & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [4]Dept Psycholol gical and Brain Sci., Univ. California, Santa Barbara, Santa Barbara, CA

Abstract: Comparing pharmacokinetics across brain sub-compartments employing high-precision intracranial measurements of psychoactive drugs
Knowledge of the pharmacokinetics of psychoactive drugs in brains remains incomplete on a number of dimensions, particularly due to a reliance on techniques limited by poor temporal resolution. To address these issues, we have developed electrochemical aptamer-based biosensors (EABs) that are capable of supporting seconds-resolved, real-time measurements of the drugs in the brains of living subjects. Specifically, using such sensors, we achieve low or sub-micromolar limits of detection with few-second temporal resolution which are capable of reliably determining the pharmacokinetics of single subjects. Here, we address the question of differences in pharmacokinetics in sub-regions of the brain, specifically between the ventricular system and solid brain tissues. To address this question, we employed novel biosensors against a general anesthetic and a psychomotor stimulant which were implanted into lateral ventricle or either the hippocampus or striatum. Followed by intravenous drug delivery, we monitored drug concentrations in the brain with ~12s temporal resolution. The availability of such high temporal resolution allowed us to accurate quantify transport kinetics and detect differences between brain regions. The simultaneous collection of dual in-brain measurements using EAB sensors enables high-precision estimates of the key pharmacokinetic parameters describing transport from the brain tissue to the ventricle in individual animals. Notably, initial detection of the drug and time to peak concentration (Tmax) was faster in the ventricular system compared to solid tissue however no differences were observed for the levels of peak concentration (Cmax). This research direction provides a chance to explore the assumptions almost universally employed in prior compartmental models of drug transport, allowing us to quantitatively address (rather than simply assume), for example, how procaine is metabolized in the central nervous system.

Disclosures: K. Wang: None. **K. Honeywell:** None. **N.A. Emmons:** None. **T.E. Kippin:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.22/T9

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIDA

Title: Beyond Dose-Response Analyses: Quantifying Pharmacokinetic Contributions to Individual Subject Variability in Response to Cocaine

Authors: *K. M. HONEYWELL, K. WANG, M. R. STOCCO, J. GERSON, N. A. EMMONS, T. E. KIPPIN;
Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Cocaine is a highly addictive psychoactive compound that has a short half-life and induces psychomotor stimulation. There has been limited attention to the role pharmacokinetics

play in psychopharmacology in general despite the growing appreciation of its importance in addiction processes. Much of this gap is due to the lack of techniques to monitor drug levels with the appropriate, behaviorally relevant temporal resolution Here, we adopted an electrochemical aptamer based (EAB) sensor with a temporal resolution of 15 s to the task of measuring in brain cocaine concentrations in awake, freely behaving animals. In this experiment, rats were given an intravenous infusion of cocaine while we simultaneously monitored in brain cocaine concentration and locomotion. A second identical test was performed one week later to assess the stability of the pharmacokinetics and response to cocaine in individual subjects. Our novel EAB for cocaine captures in brain pharmacokinetics on an individual basis such that peak concentrations and eliminations can be examined as between-subjects factors. Cocaine pharmacokinetics also positively correlated across the two sessions. Cocaine concentrations positively correlated with individual locomotor behaviors, and the area under the curves (*AUC*s) of cocaine concentrations across time positively correlated with total locomotor behaviors from the beginning of the infusion to the end of the measurement. In conclusion, our EAB sensor for cocaine can determine the individual in brain cocaine concentrations in high resolution in behaving animals enabling detailed concentration-response analyses. Such concentration-based analyses offer to transform behavioral neuropharmacology by parsing the pharmacokinetics and pharmacodynamic contributions to drug response, including elucidating their relative roles in variability of drug response across individuals.

Disclosures: K.M. Honeywell: None. **K. Wang:** None. **M.R. Stocco:** None. **J. Gerson:** None. **N.A. Emmons:** None. **T.E. Kippin:** None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.23/T10

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

Support: DTRA CB11397

Title: Development of assays for novel reactivators of organophosphorus-inhibited human acetylcholinesterase

Authors: *W. SMITH[1,2];
[1]USAMRICD, Middle River, MD; [2]ORISE, Oakridge, TN

Abstract: The use of chemical warfare agents poses a great threat to both the warfighter and civilian populations. Organophosphorus nerve agents (OPNAs) inhibit acetylcholinesterase (AChE) via a covalent interaction in the active site, causing a buildup of excess acetylcholine (ACh) in the synaptic cleft. This excess ACh results in a systemic cholinergic crisis that clinically manifests as a conglomeration of adverse effects that can eventually lead to death if left untreated. *In vitro* assays have been established as a part of the Improved Nerve Agent

Treatment System: New and Emerging Reactivator Development Screening (INATS NERDS) at the United States Army Medical Research Institute of Chemical Defense. These assays serve as a preliminary evaluation for potential reactivator compounds submitted to the INATS NERDS and the resulting data can also be used to inform the development of subsequent novel drug candidates. The employment of several generations of liquid handling robotic systems over the years has contributed to the evolution of these assays. In conclusion, these assays allow for the rapid, high throughput evaluation of not only the efficacy of novel reactivator compounds but also several biochemical parameters.

Disclosures: W. Smith: None.

Poster

PSTR143: Biochemical and Molecular Technologies I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR143.24/T11

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

Support: DTRA CB11397

Title: Developing an assay to further elucidate the interactions of chemical warfare agents and reactivators with acetylcholinesterase

Authors: *C. VAN ACKER[1,2];
[1]USAMRICD, Gunpowder, MD; [2]ORISE, Oak Ridge, TN

Abstract: Organophosphorus nerve agents (OPNAs) inhibit acetylcholinesterase (AChE) via a covalent interaction at the active site, leading to a buildup of acetylcholine (ACh) in the neuronal synapse. This buildup of ACh leads to a systemic cholinergic crisis with clinically adverse effects that can eventually lead to death if left untreated. Present countermeasures include atropine (an antimuscarinic), diazepam (an anticonvulsant), and pralidoxime (a reactivator of OPNA-inhibited AChE). Pralidoxime and similar compounds are the only countermeasures that treat the cause of OPNA intoxication and designing molecules with improved reactivation activity is an active field of research. A modified Ellman's assay measuring the innate enzyme activity of AChE is the research field's cornerstone reporter system used to elucidate the Michaelis-Menten-like kinetics of the productive interactions of reactivator molecules with OPNA-inhibited AChE. Empirical observations of naïve and OPNA-inhibited AChE behavior during standard reactivation kinetics assays suggest that the inherent stability of the enzyme may be affected by the interactions of OPNAs and/or reactivator compounds. Previously, in research conducted in other enzyme systems, fluorescent dyes combined with thermal denaturation have been utilized to study protein stability as it relates to ligand interactions. Use of a similar assay technique would provide further insight into the behavior of AChE upon interaction with OPNAs and/or reactivators. The resulting data regarding the structure-activity relationships of AChE and

a variety of small molecules could lead to the development of improved treatments for OPNA exposures in both the warfighter and civilian populations.

Disclosures: C. Van Acker: None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.01/T12

Topic: I.06. Computation, Modeling, and Simulation

Support: 1R01NS130126

Title: Electrophysiological diversity and input-output properties of human neocortical inhibitory cell-types

Authors: *P. WONG[1], Y.-T. WU[3], C. ANASTASSIOU[2];
[1]Cedars-Sinai Med. Ctr., LOS ANGELES, CA; [2]Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]Cedars Sinai Med. Ctr., Los Angeles, CA

Abstract: Inhibitory interneurons account for 20-30% of neurons in the human neocortex (Markram et al. 2004). Recent efforts have gathered a wealth of multimodal (transcriptomics, electrophysiology and morphology) cellular data for these inhibitory interneurons (Lee et al. 2023), allowing us to group them into putative classes (Gouwens et al. 2020). However, the functional roles of these distinct classes of inhibitory cell-types are not yet well understood. To characterize the computations of the different cell-types, we investigate the input-output transformations brought about by two types of stimuli to these neurons: somatic current-clamp input (DC of varying amplitude) and synaptic input along their dendrites. Our study uses a simulation-led approach utilizing multi-objective evolutionary optimization to develop biophysically realistic single-neuron models for four major inhibitory cell-types: Pvalb, Vip, Sst, and Lamp5. The biophysical models accurately reproduce observed experimental electrophysiological features and differences across the cell-types, such as the frequency-current (F-I) relationship for current-clamp experiments. Through simulations, we then inject Poisson spike trains of synaptic inputs at dendrites and measure the output at the soma. This allows us to investigate the mapping of signals from dendrites to the soma, obtaining a "frequency-lambda (F-λ) relationship" that relates synaptic input rates to firing activity. Using this framework, we characterize the responses to inputs at dendrites for each inhibitory cell-type as well as differences in electrophysiological features within cell-types across human cortical layers. While the biological implications of these differences are still unknown, our simulations provide a methodology to systematically probe the computations different classes of cell-types perform at both the single neuron and circuit level.

Disclosures: P. Wong: None. **Y. Wu:** None. **C. Anastassiou:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.02/U1

Topic: I.06. Computation, Modeling, and Simulation

Support: 1R01NS120300
Allen Institute
The Tiny Blue Dot Foundation

Title: Cell type-specific and area-dependent entrainment effects to sinusoidal electric stimulation in vivo

Authors: *I. REMBADO[1], S. LEE[1], L. MARKS[1], C. KOCH[1], C. ANASTASSIOU[2];
[1]Allen Inst., Seattle, WA; [2]Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Electrical stimulation (ES) of the central nervous system (CNS) is a widespread tool used for therapeutic interventions in numerous neurological disorders. Despite its broad use, an important limitation is that ES is applied with little to no consideration for the remarkable diversity of cell types comprising neural circuits and their differential response. This, in turn, severely limits the efficacy, interpretation, and further refinement of ES as a basic science tool and as a therapeutic translational intervention. Here, we address the fundamental question of whether and how ES can entrain specific cell types *in-vivo*. To do so, we impose a sinusoidal bipolar ES onto mouse primary visual cortex (V1) in head-fixed animals, testing several different frequencies (1-140 Hz) and amplitudes (from 1 to 5 μA). We record with ipsilateral Neuropixels probes inserted in different cortical areas, characterizing both proximal (< 300 μm) and distal (< 3 mm) evoked voltages. Our experiments characterize the effects of sinusoidal ES *in-vivo* and reveal several novel cell type-specific and area-dependent entrainment effects in different cortical structures. We apply small ES amplitudes (compared to what is typically applied in the clinical setting), which result in broadly unchanged spike rates across classes and areas vs. control. However, even this weaker ES significantly alters spike-phase coupling of units across the entire ipsilateral space and furthermore, does so with cell type specificity. In addition, we find robust within-cluster-separations emerge independent of spatial location, pointing to the selective entrainment of local subpopulations. We conclude that sinusoidal ES elicits robust and selective spike-phase modulation of cell types across the ipsilateral brain while keeping overall excitability unchanged. This points to a novel method for generating cell type-specific, cross-areal temporal communication based on spike-phase relationships.

Disclosures: I. Rembado: None. **S. Lee:** None. **L. Marks:** None. **C. Koch:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Intrinsic Powers. **C. Anastassiou:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.03/U2

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1R01NS130126

Title: Cell-type specific signatures in extracellular recordings of human MTG

Authors: *V. CERVINCHI[1], P. WONG[2], Y.-T. WU[3], C. ANASTASSIOU[4];
[1]Neurosurg., Cedars-Sinai, Los Angeles, CA; [2]Cedars-Sinai Med. Ctr., Los Angeles, CA;
[3]Cedars Sinai Med. Ctr., Los Angeles, CA; [4]Neurosurg., Cedars Sinai Med. Ctr., Los Angeles, CA

Abstract: Cell-type specific signatures in extracellular recordings of human MTGAuthors:Vitalie Cervinschi[1,2], Yuan-Ting Wu[2,3], Philip Wong[1,2], Costas A. Anastassiou[1-3]
[1] Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA [2] Department of Biomedical Science, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA [3] Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA**Disclosures:Vitalie Cervinschi**, **Yuan-Ting Wu**, **Philip Wong**, **Costas A. Anastassiou**: None**Abstract**Advances in single-cell data acquisition (transcriptomics, electrophysiology and morphology)have helped uncover the cellular taxonomy in various brain regions. However, discerning thevarious cell types from *in vivo* extracellular electrophysiology recordings during behaviourremains problematic leaving the role of cell types to human cognition and behaviourunanswered. The main limitation is the lack of a ground-truth data set linking cell typeidentity with extracellular unit properties such as spike waveform and activity characteristics.This is particularly true in human where the cell type identity cannot be interrogated throughmethods available in rodents (e.g. optotagging experiments).To meet this requirement, we use an open-access patch-seq repository featuring 63 humanmedial temporal gyrus neurons with their transcriptomic cell type and use multi-objectiveevolutionary optimization algorithms to generate 2200 biophysically realistic single-neuronmodels representing four key GABAergic cell classes, Pvalb, Vip, Sst, and Lamp5. Thesemodels, beyond recapitulating various intracellular electrophysiology properties, accuratelyemulate the extracellular signatures of single-cells [Mosher et al. 2020; Wei et al. 2023]. Wesimulate the response of these models to different stimuli and record their extracellular tracesextracting extracellular features as for *in vivo* experiments. We then use the extractedextracellular features with the associated transcriptomic cell class labels to define templatesfor training machine-learning classifiers. Finally, we deploy the model-based classifiers onunits recorded in the dorsolateral prefrontal cortex of human patients using high-densityNeuropixels probes [Paulk et al., Nat Neurosci., 2022] to infer the label of *in vivo* units andidentify their role during cortical processing in the human brain *in vivo*.

Disclosures: V. Cervinchi: None. **P. Wong:** None. **Y. Wu:** None. **C. Anastassiou:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

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Program #/Poster #: PSTR144.04/U3

Topic: I.06. Computation, Modeling, and Simulation

Support: Grant 1R01NS130126
Cedars Award AWD00001172

Title: Bio-realistic simulation and optimization of electrical stimulation protocols and their application in human DBS patients

Authors: *K. KOZALAKIS, Y.-T. WU, A. MILLER, A. N. MAMELAK, C. A. ANASTASSIOU;
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Abstract: Electrical stimulation (ES) is used extensively in both research and clinical settings for modulating brain activity. Despite its extensive use, the precise biophysical mechanisms through which ES induces its effects in the brain remain unclear. The lack of insight into the fundamental ES mechanisms leading to neuromodulation severely limits the effectiveness of ES as a therapeutic tool. Here we study the fundamental mechanisms of ES on human cells of major cortical cell-types *in silico*. We perform a comprehensive investigation of cell-type- and ES-related factors, aiming to develop targeted ES waveforms that selectively entrain individual cells and cell-types in brain circuits *in vivo*. We develop and deploy biophysical bio-realistic single-neuron models from open-access human data sets containing electrophysiology, morphology and transcriptomics. We test biophysically realistic models of major excitatory and inhibitory human cell classes in simulations with varying ES parameters (e.g., ES frequency, field type), investigating how different ES parameters interact with single-neuron models. Simulations demonstrate that the models replicate cell-type-specific ES effects observed in human *in vitro* experiments and show that spike-field entrainment to sinusoidal ES does not depend on a specific ion channel or conductance but is a generic property spanning across cell-types [Lee, Kozalakis et al, Neuron, 2024]. In a second step, we develop a computational framework based on evolutionary optimization of spike-field entrainment metrics, to develop and finetune ES stimulation parameters that selectively target and entrain human cell types in a controlled manner. Importantly, the study progresses beyond *in silico* simulations, and tests these new ES protocols and associated metrics in human intracranial experiments conducted *in vivo*, in patients undergoing DBS surgery where cortex is stimulated and subcortical single unit spiking is recorded simultaneously. We expect these tools to decisively contribute toward the development of improved ES-based therapies.

Disclosures: K. Kozalakis: None. **Y. Wu:** None. **A. Miller:** None. **A.N. Mamelak:** None. **C.A. Anastassiou:** None.

Poster

PSTR144: Cellular Models

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.05/U4

Topic: I.06. Computation, Modeling, and Simulation

Support: NINDS U01 NS113873
NIDDK R01 DK120824

Title: Afferent transmission block by Dorsal Root Ganglion and Peripheral Nerve Stimulation: a computational modeling study

Authors: *S. RIGI LADEZ, J. LIU, L. CHEN, B. FENG;
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Abstract: Chronic pain is a major global health issue, poorly managed by current pharmacological therapies like opioids, which contribute to prescription drug abuse. Neuromodulation as a non-drug alternative for treating chronic pain can only benefit a fraction of patients and does not provide consistent pain relief, which is likely caused by our limited understanding of the underlying mechanisms of neuromodulation. We recently implemented single-fiber recordings to demonstrate the afferent blocking effect by sub-kilohertz electrical pulse stimulation of the dorsal root ganglia (DRG), a potential mechanism to account for the pain-relieving effect of DRG stimulation without eliciting paresthesia in some patients. In addition, sub-kilohertz peripheral nerve stimulation (PNS) also reversibly blocked axonal transmission of unmyelinated C-fibers and thinly myelinated Aδ-fibers. In this study, we conducted a computational modeling study to recapitulate the afferent blocking effect of DRG stimulation and PNS using the NEURON simulation environment. Our sensory afferent models incorporate a comprehensive set of voltage-gated sodium (NaV1.6 - 1.9), potassium (A-type, delayed rectifier, Ca^{2+}-activated), and calcium (L, T-type) channels, including Markov gating for NaV1.6/1.7. Simulations track activity-dependent changes in intra-axonal ion concentrations from transmembrane ionic currents and axial diffusion in the intra-axonal space. Our simulation results indicate that both DRG stimulation and PNS cause a significant increase in intra-axonal Na+ concentration and a reduction in K+ concentration, collectively disrupting the trans-axonal ionic gradients. This disruption resulted in activity-dependent conduction slowing, leading to the eventual conduction block in both Aδ- and C-fiber afferents. In addition, calcium-activated potassium channels (BK and SK) also played a contributing role to the transmission block by hyperpolarizing the membrane potential. This computational modeling study has laid a solid foundation in understanding the intricate mechanisms underlying DRG stimulation and PNS, presenting a framework for the in-silico design of future neuromodulatory protocols that target the peripheral afferents to treat chronic pain.

Disclosures: S. Rigi Ladez: None. **J. Liu:** None. **L. Chen:** None. **B. Feng:** None.

Poster

PSTR144: Cellular Models

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.06/U5

Topic: I.06. Computation, Modeling, and Simulation

Support: Enterprise Ireland Innovation Partnership Grant in collaboration with Boston Scientific Ltd

Title: Effect of position and orientation of branching collaterals on activation of hyperdirect pathway neurons during STN DBS

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Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective, clinically approved method of symptom control for patients with Parkinson's disease. It can, however, induce side effects that limit efficacy and decrease patients' quality of life. These can range from motor side effects, including reduced speech fluency and dyskinesia, to psychiatric ones, such as depression and disinhibition. Reducing stimulation-induced side effects while maintaining symptom control requires careful targeting of neural structures. Computational modeling of the electric potential surrounding the electrode and the neural response to stimulation enables the region of activation to be predicted and facilitates optimization of stimulation parameters to target specific regions. In addition to volume conductor electrical and geometrical properties, the predicted spatial patterns of neural activation depend on individual nerve properties. Descending layer V pyramidal tract fibers of the hyperdirect pathway have long been implicated in mediating the therapeutic effect of STN DBS via antidromic activation of cortical neurons [1]. Branching collaterals extending from these fibers into STN are thought to facilitate this due to their relatively low stimulation threshold. In this study, the effect of collateral and axon geometry and orientation on DBS stimulation threshold and site of activation is examined. Models are developed for both conventional symmetrical DBS electrodes and segmented leads which allow directional stimulation. Finite element models of the electric field around the electrode were implemented in COMSOL Multiphysics and coupled to a cortical axon model with branching collateral [2] implemented in NEURON. The position along the fiber and branching angle of the collateral were varied for anodal and cathodal stimulation. The activation threshold and site of activation was identified for each fiber in a spatially distributed grid surrounding the electrode, for each collateral position and orientation. The results show that the influence of geometric and morphological neuron properties on the thresholds for activation during DBS are more pronounced for anodal than cathodal stimulation. These findings highlight the importance of considering neural orientation and morphological structure for prediction of the extent of neural activation during DBS.
[1] Gradinaru et al., Science, 2009.
[2] Foust et al., Journal of Neuroscience, 2011.

Disclosures: J. Orlowski: None. **C. Byrne:** None. **M.M. Lowery:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.07/U6

Topic: I.06. Computation, Modeling, and Simulation

Title: Differentiating computational neuron models for different afferent C-fiber subtypes identified during microneurography using generalized particle swarm optimization

Authors: *A. MAXION[1], A. FIEBIG[2], E. KUTAFINA[3], A. TROGLIO[4], J. K. TIGERHOLM[1], B. NAMER[5];
[1]RWTH Aachen Univ., Aachen, Germany; [2]Inst. of Neurophysiology, RWTH Aachen University, Aachen, Germany, Aachen, Germany; [3]Inst. for Biomed. Informatics, Fac. of Med. and Univ. Hosp. Cologne, Univ. of Cologne, Cologne, Germany; [4]Res. Group Neuroscience, IZKF, Dept. of Neurophysiology, RWTH Aachen Univ., Aachen, Germany; [5]Uniklinik RWTH Aachen, Aachen, Germany

Abstract: Unmyelinated afferent peripheral nerve fibers (C-fibers) play an important role in several diseases in humans such as small fiber neuropathy and diabetes. Therefore, it is crucial to understand the functioning of these nerve fibers. C-fibers can be further divided into several subclasses depending on their excitation patterns and reaction to mechanical stimuli and serve different functional roles: Mechano-sensitive (CM), mechano-insensitive (CMi), and fibers with a very high mechanical threshold (VHT). Microneurography (MNG) can be used to record the extracellular activity of C-fibers in awake humans, providing valuable insights into neural function. A key characteristic of C-fibers is activity-dependent conduction velocity slowing, which varies with the C-fiber subtype and length. Altered molecular mechanisms, such as ionic currents, may explain the differences of the C-fiber subtypes. However, with MNG it is not possible to assess these mechanisms. Therefore, we explore these mechanisms utilizing a multicompartmental neuron model, implemented in the simulation environment NEURON. This model, featuring a smaller branch axon connected to a larger parent axon to mimic peripheral nerve fiber morphology, is fine-tuned to simulate the behavior of CMi-fibers, which play an important role in neuropathic pain. We introduce an optimization algorithm that uses the Generalized Particle Swarm Optimization (GEPSO) to fit the computational model to the C-fiber subclasses. The algorithm effectively explores the parameter space by increasing interactions among particles and diversity in the swarm. In the cost function, the fit of the model is judged using MNG data. The algorithm is optimized to run on a high-performance cluster and parallelized using a message-passing interface.Our results demonstrate the model's ability to replicate MNG data across the different C-fiber subclasses showing the underlying mechanistic differences for each subclass, which are generally consistent with existing literature.Our study highlights the GEPSO algorithm's efficacy in optimizing multicompartmental neuron models, which can help to gain insights into molecular mechanisms in nerve fibers. The optimization

algorithm can easily be tailored to different MNG data, enabling the generation of personalized models for patients with altered MNG recordings and aiding in identifying potential molecular alterations. Moreover, the versatility of the GEPSO algorithm extends its applicability to other neural models, enhancing its utility in computational neuroscience research.

Disclosures: A. Maxion: None. **A. Fiebig:** None. **E. Kutafina:** None. **A. Troglio:** None. **J.K. Tigerholm:** None. **B. Namer:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.08/U7

Topic: I.06. Computation, Modeling, and Simulation

Title: Synthetic substrates enhance adherence, neural activity, and network development of in vitro neural cultures

Authors: *A. PASSARO[1], K. PARHAM[2], W. RICHARDS[3], S. A. CHVATAL[1], C. LEBAKKEN[2], R. GORDON[2];
[1]Axion BioSystems, Atlanta, GA; [2]Stem Pharm, Inc., Madison, WI; [3]R&D, Stem Pharm, Inc., Madison, WI

Abstract: Advancements in cell biology and methodology (i.e., human induced pluripotent stem cell [hiPSC] culture) and a recognition that *in vivo* models often do not effectively improve translation have contributed to a growing demand for improved *in vitro* neural models. Synthetic substrates mimicking the extracellular matrix offer several advantages over animal-derived matrices, including consistent defined composition, tunable adhesive and biomechanical properties, and the inclusion of bioactive peptides to create an optimal microenvironment and enhance cellular phenotypes. Microelectrode array (MEA) platforms are a valuable tool for electrophysiological analysis of neural cultures in a high-throughput, non-invasive manner, enabling functional assessment and comparison of phenotypes across conditions. Stem Pharm has developed chemically defined substrates that use norbornene-functionalized polyethylene glycol (PEG) and synthetic peptides offered precoated and shelf-stable on ready-to-use standard multiwell plates based on tissue culture-treated polystyrene or cyclic olefin co-polymers. One formulation, SureCoat™ SP-133, has been shown to promote adhesion and long-term cultures for multiple iPSC-derived neural cell types. Here, we validated the adherence of SureCoat SP-133 to Axion Biosystems' CytoView MEA™ plates and monitored attachment and maturation of several hiPSC-derived neural cultures, including glutamatergic neurons, GABAergic neurons, and motor neurons (MNs), via the Maestro Pro™ MEA platform. All cell types exhibited strong adherence (resistance >30 kΩ) and increasing activity and connectivity over 21 days in culture. As motor neurons can be challenging to attach for long-term cultures, we compared MNs cultured on SP-133 to poly-D-lysine (PDL), a common matrix used for MN cultures. SP-133 resulted in increased resistance (38.0±2.1 vs. 18.8±1.4 kΩ), Mean Firing Rate (4.4±0.8 vs.

2.3±0.6 Hz), and Synchrony Index (0.29±0.07 vs. 0.05±0.02; all SEM, n=6) compared to PDL at day 21 in culture. Transcriptional profiles of MNs cultured for seven days on the synthetic substrates compared to PDL demonstrated upregulation of genes associated with neuronal maturation, axon guidance, synapses and synaptic signaling. In addition, when cultured on substrate-coated polystyrene culture plates, we observed enhanced neurite outgrowth and less clumping compared to those cultured on PDL. Taken together, these results support the use of both PEG-based synthetic substrates to enhance *in vitro* cultures and functional assessment to quantify and compare phenotypes for disease modeling, drug screening, and toxicology applications.

Disclosures: A. Passaro: A. Employment/Salary (full or part-time):; Axion BioSystems. **K. Parham:** A. Employment/Salary (full or part-time):; Stem Pharm, Incorporated. **W. Richards:** A. Employment/Salary (full or part-time):; Stem Pharm, Incorporated. **S.A. Chvatal:** A. Employment/Salary (full or part-time):; Axion BioSystems. **C. Lebakken:** A. Employment/Salary (full or part-time):; Stem Pharm, Incorporated. **R. Gordon:** A. Employment/Salary (full or part-time):; Stem Pharm, Incorporated.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.09/U8

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF GRF Grant DGE-2039655

Title: Dynamical analysis of transistor-based Hodgkin-Huxley neuron circuit models

Authors: J. O. HASLER[1], S. BHATTACHARYYA[1], *S. M. BAER[2];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Sch. of Mathematics and Statistical Sci., Arizona State Univ., Tempe, AZ

Abstract: Neuromorphic engineering started with the explicit goal of building a bridge between neuroscience and engineered systems (Mead 1990). In this study, a new computational neuroscience framework is utilized to interpret physically implemented neural models on SoC FPAA devices. Specifically, we apply the transistor channel approach to construct a silicon (Si) neuron circuit analog of the Hodgkin-Huxley (HH) model and analyze the dynamics of the model using singular perturbation and bifurcation methods. Digital neuron models often encounter a significant tradeoff between biological fidelity and computational resources, such as power, time, and implementation area. This tradeoff typically renders the highly detailed HH model impractical for large-scale neuroscience exploration. Using the analogous physics governing transistors and biological ion channels, transistor-based circuit models offer resource-efficient and numerically stable emulations of the traditionally stiff HH model on analog substrates. The question becomes how close are the nonlinear dynamics, and this work employs a

dynamical systems framework to explore the behavior of transistor channel HH models across their parameter range. Experimental data generated from the physical circuit is compared and contrasted to the numerical results (digital) generated from the Si neuron mathematical model and the corresponding established Hodgkin-Huxley model. Checked for consistency is the bifurcation structure in the Si mathematical model to the Si circuit data. For both the Si mathematical model and the established HH model the direction of bifurcation is consistent, as well as dynamic bifurcation onsets (slow ramping of current). The results of this study serve as a starting point for more systematic investigations of Si neurons and networks based on realistic morphologies. This work underscores the potential of these models to facilitate large-scale, biologically realistic simulations in neuroscience research, bridging a crucial gap between computational efficiency and biological accuracy.

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Poster

PSTR144: Cellular Models

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Program #/Poster #: PSTR144.10/U9

Topic: I.06. Computation, Modeling, and Simulation

Support: NextGeneration EU PNRR MUR - M4C2 – Action 1.4 National Center for Gene Therapy and Drugs based on RNA TechnologyCN00000041 - Call Potenziamento strutture di ricerca e creazione di "campioni nazionali di R&S CUP J33C220011

Title: Unlocking vascularization potential in a 3D bioprinted neural model

Authors: *C. SANCHINI[1], E. BRANDI[3], C. SCOGNAMIGLIO[4], E. SENTURK[3], C. D'ANTONI[5], G. CIDONIO[6], G. RUOCCO[2];
[1]Inst. Italiano di Tecnologia, Rome, Italy; [2]Inst. Italiano di Tecnologia, Roma, Italy; [3]Sapienza Univ. of Rome, Rome, Italy; [4]Ctr. for Life Nano and Neuro Sci., Inst. Italiano di Tecnologie, Rome, Italy; [5]Sapienza Univ. Di Roma, Rome, Italy; [6]Dept. of Mechanical and Aerospace Engin., Univ. di Roma La Sapienza, Rome, Italy

Abstract: When compared to traditional 2D cultures, cultivating neural cells in a 3D environment better mimics the natural neuronal surroundings found in vivo, providing an optimal setting for integration, growth, and synaptic connection formation in new neurons. The well-established role of vascular development in regulating neural proliferation through the release of neurotrophic factors underscores the shared molecular signals and synergistic action between neurogenesis and angiogenesis. This supports the concept of a neurogenic niche as a functional unit bridging neural precursor cells and their environment, with blood vessels playing a pivotal role. Therefore, integrating vascularization into the bio-fabrication of 3D neural models is crucial, albeit a significant challenge in tissue engineering. Bioprinting shows promise in fabricating complex living tissues, but achieving the delicate balance between structural fidelity

and cell growth and differentiation remains challenging. Here, we characterized various neural cells within distinct biomaterials using different bioprinting techniques. Our aim is to biofabricate a neural vascularized tissue substitute using microfluidic bioprinting, intended as a platform for disease modeling and drug delivery. Neuroblastoma cells SK-N-BE(2) were encapsulated in gelatin and dECM at different concentrations. Results suggest that gelatin at 5% and dECM at 2% sustain neurite formation, promote cell survival, and allow for sufficient RNA extraction yield for qPCR analysis. Due to the low viscosity of this biomaterial alone, it was extruded through a microfluidic printhead together with a harder shell (composed of gelatin, dECM, and alginate) proposed as a biomaterial for endothelial cells. This process created a printable dual (core-shell) material that is useful for vascularizing a 3D neural model. Simultaneously, we differentiated functional cortical and dentate gyrus neural progenitors from hiPSCs, encapsulating them in two different biomaterials: gelatin-dECM and alginate-geltrex. Cortical neural progenitors encapsulated in alginate-geltrex sprouted neurites in 3D up to 4 days post-encapsulation, indicating a candidate biomaterial suitable for delicate iPSC-derived cells, to be used as a core material in our microfluidic printing strategy. In conclusion, we identified two biomaterials suitable for promoting the survival and neurite formation of neural cells, suggesting a feasible microfluidic bioprinting strategy to obtain vascularized 3D neural models. These models can facilitate the study of neurodevelopment and neurodevelopmental diseases when coupled with iPSC technology.

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Poster

PSTR144: Cellular Models

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Program #/Poster #: PSTR144.11/U10

Topic: I.06. Computation, Modeling, and Simulation

Support: DFG grant SFB1080

Title: Modelling subunit-specific AMPAR copy-number change upon plasticity induction

Authors: *S. WAGLE[1], N. KRAYNYUKOVA[1], M. KRACHT[2], A. ACKER-PALMER[1], A.-S. HAFNER[3], E. M. SCHUMAN[4], T. TCHUMATCHENKO[1];
[1]Inst. of Exptl. Epileptology and Cognition Res. (IEECR), UKB, Bonn, Germany; [2]Johann Wolfgang Goethe-University Frankfurt, Frankfurt, Germany; [3]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands; [4]Max Planck Inst. for Brain Res., Frankfurt/Main, Germany

Abstract: AMPA receptors (AMPARs) play a crucial role in mediating the expression of long-term synaptic plasticity at excitatory synapses. The strength of a synapse is considered proportional to the number of AMPARs at the post-synaptic density. Various trafficking

mechanisms, such as diffusion, active transport, endo/exocytosis, protein degradation, and local synthesis, can regulate the number of AMPARs at different dendritic locations [1]. More recent work also suggests that auxiliary subunits, such as TARPs and Cornichons, affect the functional properties and trafficking of AMPARs [2]. In this study, we combined computational modeling with experimental data to elucidate which trafficking steps are essential to explain the experimentally observed localizations of AMPARs and the response of different AMPAR subtypes to plasticity. Specifically, we determined the global transport (diffusion and drift constants) parameters by fitting our model to GluA2 fluorescence intensity measured along dendrites. We found that active transport is essential to explain the observed protein distribution. Then, we conducted fluorescent labeling of endogenous GluA2, and using our model, estimated that the GluA2 endocytosis rate exceeded the exocytosis rate, with their ratio being constant along the dendrites. We also found that the synaptic enrichment of GluA2, as the fluorescence intensity ratio between the spine and shaft surface, was ~ 1 and increased with the dendritic distance. A recent study used ribosomal profiling and micro-dissection of soma and neuropil and found that several auxiliary subunits of the TARP family were predominantly translated in the soma [3]. Using a similar set of approaches, we found that one of the prominent auxiliary subunits of AMPARs, TARP-γ8, was mainly synthesized in the soma. In contrast, another auxiliary subunit, CNIH2, showed significant local translation in dendrites, which was further enhanced after plasticity induction (chem-LTP). Interestingly, disrupting CNIH-2 trafficking using shRNA knockdown reduced surface insertion of nascent GluA2 subunits but not GluA1 subunits of AMPARs. Finally, we used this GluA2 subunit selectivity of CNIH2 in our model as a potential mechanism to explain the difference in temporal response of two sub-types of AMPARs, namely the calcium-permeable (GluA2-lacking) and calcium-impermeable (GluA2-containing) AMPARs, upon plasticity induction. **References:** [1] Diering, G.H., and Huganir, R.L. (2018). Neuron *100*, 314-329. [2] Bissen, D., Foss, F., and Acker-Palmer, A. (2019). Cel. and Mol. Life Sciences, 76:2133-2169.
[3] Glock et al. (2021) PNAS 118 (43) e2113929118

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Poster

PSTR144: Cellular Models

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Program #/Poster #: PSTR144.12/U11

Topic: I.06. Computation, Modeling, and Simulation

Support: Project Identification No. RTI 4006, Department of Atomic Energy, Government of India

Title: Decoding the mechanisms behind a commonly ignored electrophysiological feature - the Depolarization Baseline Offset

Authors: *A. KUMAR[1], A. SHAHUL[2], U. S. BHALLA[3];
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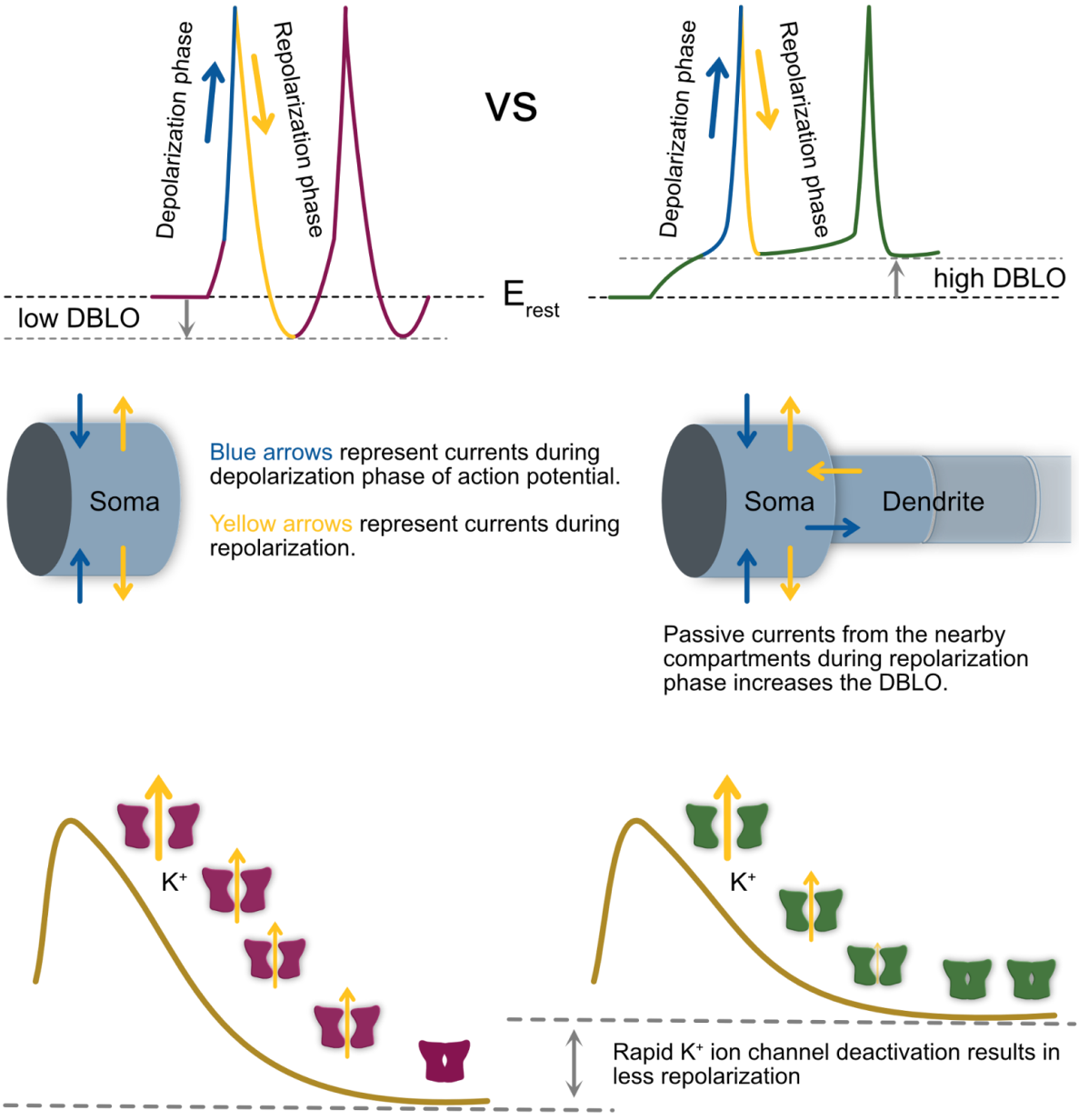
Abstract: Despite years of research aimed at deciphering the electricalproperties of neurons, our current understanding of some of these propertiesremains incomplete. One such significant yet often overlooked property in manyneurons, especially in pyramidal neurons, is the Depolarization Baseline Offset(DBLO) - the change in the baseline membrane potential during a train of actionpotentials (AP) induced by current injections into the soma. Limitedunderstanding of the phenomenon has resulted in many state-of-the-artconductance-based models of CA1 pyramidal neurons not demonstrating the highlevels of DBLO observed in experiments.To bridge this knowledge gap, we conducted unbiased stochasticparameter searches on experimentally-constrained, conductance-based neuronalmodels in the neuronal simulator MOOSE. Our investigations corrected for errorsin membrane potential recordings arising from liquid junction potentials, acritical oversight in prior studies. Our findings indicate a minimal influenceof ion channel distribution at the axon initial segment, and the reversalpotential of the delayed rectifier potassium channel (K_DR) on DBLO. Instead,our analyses reveal that models with experimentally constrained impedanceamplitude profiles exhibited higher passive back-propagating currents fromdendrites to soma during the repolarization phase of an AP, resulting in highDBLO. Modifications in transient sodium channel kinetics and the incorporationof rapidly deactivating K_DR also result in high DBLO. Neglecting DBLO whilebuilding realistic neuronal models can lead to inaccurate ion channelexpression and misinterpretations of their roles in variouselectrophysiological phenomena, such as the role of persistent sodium channelsin firing bistability. The improved models resulting from our study may not only advanceour understanding of neuronal computations but also inform the development ofnovel therapeutic strategies for disorders stemming from aberrant neuronalelectrical properties.BioRxiv link: https://doi.org/10.1101/2024.01.11.575308



Disclosures: A. Kumar: None. **A. Shahul:** None. **U.S. Bhalla:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.13/U12

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH grant R03NS130387

Title: A novel method to restore conductance in a locally demyelinated axon using magnetic stimulation

Authors: *H. YE[1], Y. CHEN[1], J. CHEN[2], J. HENDEE[1];
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Abstract: Axonal demyelination leads to failure of axonal conduction. Current research on demyelination focuses on the promotion of remyelination. Electromagnetic stimulation is widely used to promote neural activity. We hypothesized that electromagnetic stimulation of the demyelinated area, by providing excitation to the nodes of Ranvier, could rescue locally demyelinated axons from conductance failure. We built a multi-compartment NEURON model of a myelinated axon under electromagnetic stimulation. We simulated the action potential propagation in myelinated axons and observed conductance failure when local demyelination occurred. Conductance failure was due to current leakage and a lack of activation of the nodes in the demyelinated region. To investigate the effects of microcoil stimulation on locally demyelinated axons, we positioned a miniature coil next to the affected area to activate nodes in the demyelinated region. Subthreshold microcoil stimulation caused depolarization of node membranes. This depolarization, in combination with membrane depolarization induced by the invading action potential, resulted in sufficient activation of nodes in the demyelinated region and restoration of axonal conductance. The restored axonal conductance was due to the enhanced Na + current and reduced K + current in the nodes rather than a reduction in leakage current in the demyelinated region. Finally, we found that microcoil stimulation had no effect on axonal conductance in healthy myelinated axons. Activation of nodes in the demyelinated region using electromagnetic stimulation could provide an alternative treatment strategy for demyelinating diseases.

Disclosures: H. Ye: None. **Y. Chen:** None. **J. Chen:** None. **J. Hendee:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.14/U13

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-NIDCD R01 DC012347

Title: Simulation of quantal transmission and glutamate diffusion using COMSOL: application to extended synaptic clefts

Authors: A. GOVINDARAJU[1], ***R. RAPHAEL**[2];
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Abstract: Auditory and vestibular hair cells possess synaptic ribbons at defined locations that coordinate fast localized release of glutamate. The reason for the precise location of ribbon synapses in these cells is not well understood but is likely related to the ability of glutamate to diffuse in the synaptic cleft and the nanoscale organization of the pre and post synaptic membranes. Glutamate accumulation has also been hypothesized to affect quantal transmission. To test these hypotheses, we expanded our previous model of the vestibular hair cell calyx (VHCC) synapse (Govindaraju et al 2023) to include a mechanistic, finite element model of quantal transmission. The VHCC synapse encodes head motion signals and is characterized by an extended synaptic cleft formed by the apposition of pre- and post-synaptic membranes with up to 90% of the basolateral surface of the sensory hair cell surrounded by the afferent terminal. To simulate transmission between sensory cell and afferent neuron, our model uses ion currents based on whole-cell recordings, continuity equations to describe changes in electric potential within hair cell, synaptic cleft, afferent fiber. The geometry of the synapse was created in COMSOL Multiphysics (a finite element software) with glutamate release sites and post-synaptic density (PSD) located on surfaces representing the pre-synaptic and post-synaptic membranes. 2000-8000 glutamate ions are released per vesicle following a gaussian pulse. Electro-diffusion equations are used to model [K^+], [Na^+] and glutamate [Glu^-] diffusion in the synaptic cleft. Postsynaptic AMPAR conductance densities were defined at PSDs and the proportion of receptors open is a function of glutamate concentration in the vicinity. AMPAR kinetics and associated parameters were adapted from the literature (Rusakov et al. 2007; 2011). Initially we simulate glutamate release independent of pre-synaptic depolarization. These additions to the VHCC model predict EPSCs and EPSPs as a function of glutamate release, diffusion and AMPAR activation. The predictions are compared with experimentally observed quantal EPSCs and EPSPs. The implementation of quantal transmission using COMSOL Multiphysics will allow the study of both calyceal and bouton fiber responses to stimuli activating cells in the tightly packed vestibular epithelia. This approach allows for investigation of interactions between quantal and ephaptic (nonquantal) transmission at the VHCC synapse and can be adapted to study other cells. Supported by NIH-NIDCD R01 DC012347

Disclosures: A. Govindaraju: None. **R. Raphael:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.15/U14

Topic: I.06. Computation, Modeling, and Simulation

Title: Generation of Neuro293's by knockout of the RE1 Silencing Transcription Factor (REST/NRSF) in HEK293 cells enables high-transcriptional activity through neuron-restricted promoters and efficient interrogation of human neuronal protein networks and functions in vitro

Authors: *J. MOSES[1], C. BOSSE-JOSEPH[1], A. N. STEWART[2];
[1]Univ. of Kentucky, Lexington, KY; [2]Physiology/SCoBIRC, Univ. of Kentucky, Lexington, KY

Abstract: In the practice of cell culture, immortalized cell lines such as SH-SY5Y human neural blastoma cells, are thoroughly used in experimentation. However, factors including the absent expression of mature neuronal proteins in undifferentiated cells, the time needed for differentiation, and relative rate of growth limit experimental paradigms to evaluate mature neuronal proteins create a barrier of difficulty when attempting to conduct medium-to-high throughput in vitro experiments. In contrast, the use of the immortalized cell line of human embryonic kidney cell 293 line (HEK293), have become an invaluable tool to interrogate molecular biology and biochemistry across a wide spectrum of science. HEK293 have the ability to express a high abundance of proteins, grow at exceptional speeds, and possess high efficacy for plasmid transfection. The capacity to express transgenes and the ease of assimilating plasmids makes HEK293s favored for biochemical interrogation as well as for being used as a tool to package viral particles. In efforts to truncate the challenges with producing mature neuronal proteins in immortalized cell lines, we knocked out the RE1-Silencing Transcription factor (REST) in HEK293's to create a new neuron-like cell line named Neuro293. Our developed Neuro293's express mature neuronal protein networks without subjugation to neuronal-differentiation paradigms while maintaining growth capacity. We validate the upregulation of pre-/post-synaptic proteins, voltage gated ion channels, synaptic vesicle-associated, and neuron-specific cytoskeletal proteins at both the transcriptional (RNAseq) and translational (western blot and immunocytochemistry) levels. When used to test the expression of transgenes through neuron restricted promoters, we demonstrate an upregulation of both the Syn1 and CamK11b promoter activity, enabling the interrogation and *in vitro* modeling of AAV plasmid constructs. We present morphological comparison between normal HEK293's and our Neuro293's pre- and post-exposure to neuronal-differentiation conditions as well as demonstrate the excitability through calcium imaging. Collectively, we propose Neuro293's as a robust and invaluable tool for the biochemical interrogation of mature neuronal proteins in a medium-to-high throughput manner that can also be used to save time and money by testing neuron-restricted viral vectors *in vitro* prior to applying *in vivo*.

Disclosures: J. Moses: None. **C. Bosse-Joseph:** None. **A.N. Stewart:** None.

Poster

PSTR144: Cellular Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR144.16/U15

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIMH Grant P50MH132642

Title: Sleep and waking dynamics in a biophysical thalamocortical cell model

Authors: *K. MCGAHAN, M. M. MCCARTHY, N. J. KOPELL;
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Abstract: Although thalamic dynamics in sleep have been much studied, the cause and role of the awake thalamic alpha rhythms is not well understood. Previous thalamic mathematical models have either ignored awake alpha rhythms as being outside of their research scope, or used an ionic current that is not found experimentally in order to produce the necessary high-threshold alpha bursts. Here we show that high and low threshold bursting can be produced in a single thalamocortical (TC) cell model. Our proposed model uses only currents validated with expression data from the Allen Brain Institute. One surprising feature of this model is the importance of the M-current, something excluded from previous TC cell models, in obtaining these complex dynamics. The inclusion of an M-current provides new insights into how TC cells might interact and function in response to neuromodulators such as acetylcholine. Using parameter search algorithms we find other unique experimentally observed firing behaviors not seen with the current TC cell models. The mathematical analysis presented here details the role each ionic current has in maintaining the different firing regimes. Our analysis reveals that while some currents are vital for the full range of dynamics, some ion channels' internal kinetics cause them to interact with only the high or low threshold behaviors, but not both. This analysis proposes the idea that these cells can be regulated to finely tune one type of dynamics without adversely influencing the other neuronal properties. Additional simulations of pharmacology experiments, and an exploration of the model's bifurcation structure, identifies how TC cells transition between these regimes in clinically relevant and experimentally testable manners. This fully mechanistic TC cell model may serve as the new foundation for future computational studies that depend on capturing the entire range of observed thalamocortical cell dynamics.

Disclosures: K. McGahan: None. **M.M. McCarthy:** None. **N.J. Kopell:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.01/U16

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R00EY032179

Title: Poisson variational autoencoder: combining bayesian inference with predictive coding results in amortized sparse coding

Authors: *H. VAFAII[1], D. GALOR[1], J. L. YATES[2];
[2]Vision Sci. & Optometry, [1]UC Berkeley, Berkeley, CA

Abstract: Variational autoencoders (VAE) employ Bayesian inference to interpret sensory inputs, mirroring processes that occur in primate vision across both ventral (Higgins et al., 2021) and dorsal (Vafaii et al., 2023) pathways. Despite their success, traditional VAEs rely on continuous latent variables, which significantly deviates from the discrete nature of biological neurons. Here, we developed the Poisson VAE (P-VAE), a novel architecture that combines

principles of predictive coding with a VAE that encodes inputs into discrete spike counts. Combining Poisson-distributed latent variables with predictive coding introduces a metabolic cost term in the model loss function, suggesting a relationship with sparse coding. We explored this connection, training a P-VAE with a linear decoder and an overcomplete latent space on natural image patches, contrasting it with a traditional Gaussian VAE. Unlike the Gaussian VAE, which learned features similar to principal component analysis, P-VAE exhibited Gabor-like feature selectivity, reminiscent of sparse coding patterns. Additionally, we analyzed the geometry of learned representations. We found that the P-VAE encodes its inputs in relatively higher dimensions, facilitating linear separability of categories in a downstream classification task. Our work provides an interpretable computational framework to study brain-like sensory processing and paves the way for a deeper understanding of perception as an inferential process.

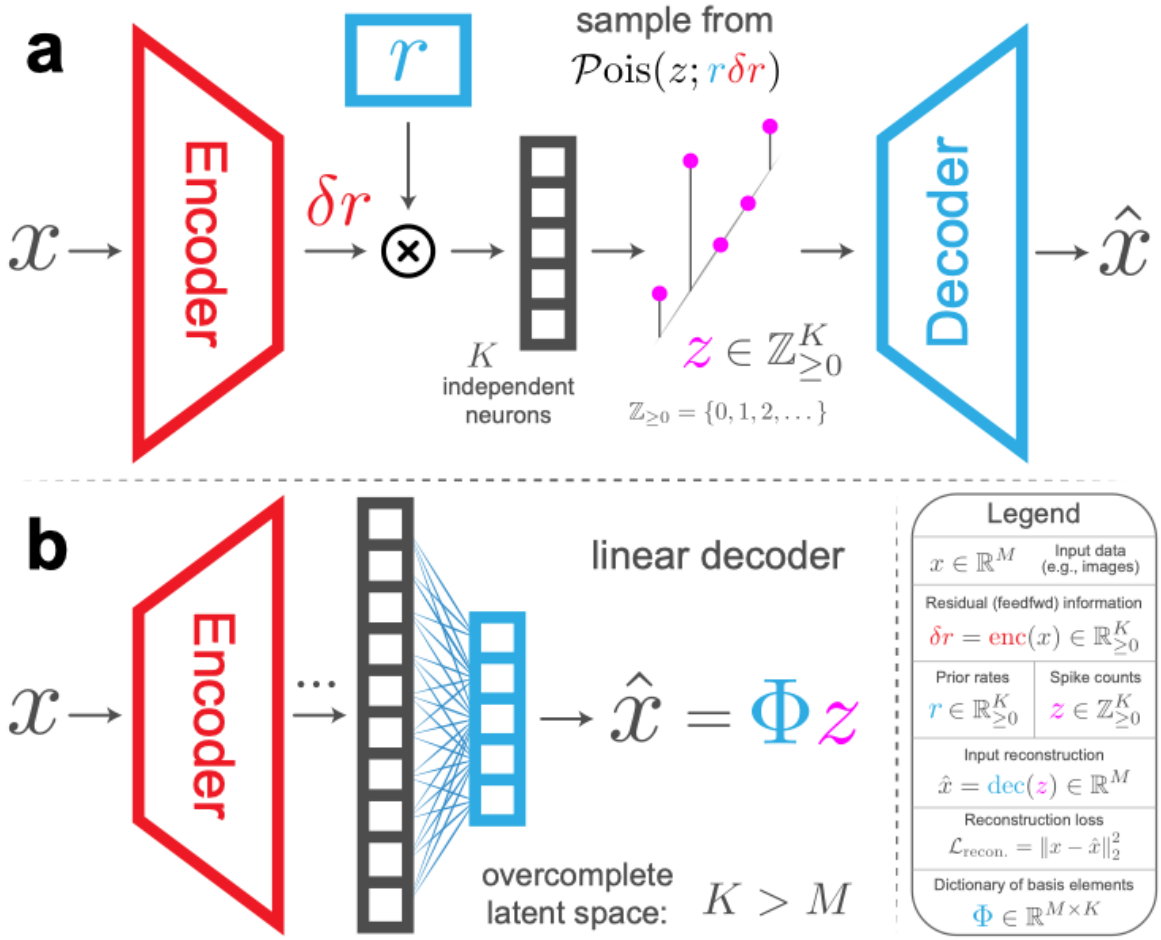

Figure 1: Introducing the Poisson VAE ($\mathcal{P}$-VAE). **(a)** Model architecture. Colored shapes depict learnable model parameters, including the prior firing rates, $\boldsymbol{r}$. We color code the model's inference and generative components using red and blue, respectively. The $\mathcal{P}$-VAE encodes its inputs in discrete spike counts, $\boldsymbol{z}$, significantly enhancing its bio-realism. **(b)** "Amortized Sparse Coding" as a special case of the $\mathcal{P}$-VAE.

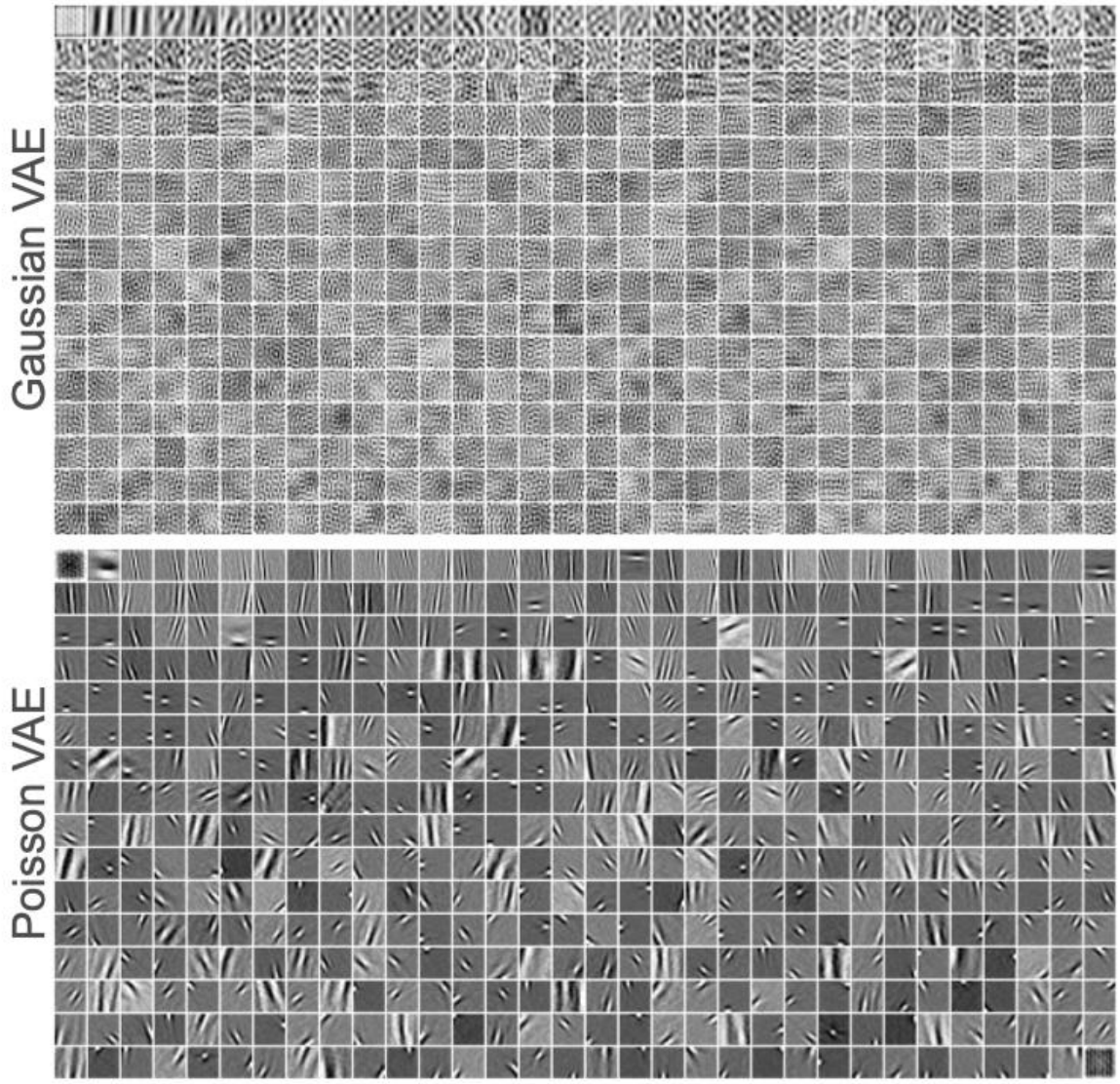

Figure 2: Learned basis elements (512 total, each made of $16 \times 16 = 256$ pixels. In other words, $\Phi \in \mathbb{R}^{256 \times 512}$). Features are ordered from top-left to bottom-right, in ascending order of their associated variance, σ^2, and, prior firing rate, r, for Gaussian and Poisson VAEs, respectively.

Disclosures: H. Vafaii: None. **D. Galor:** None. **J.L. Yates:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.02/U17

Topic: I.06. Computation, Modeling, and Simulation

Support: SPP 2205

Title: Robustness and evolvability in a pattern recognition network model

Authors: *D. CHO[1,2], J. CLEMENS[1,3];
[1]ENI-G, a Joint Initiative of the Univ. Med. Ctr. Göttingen and the Max Planck Inst. for Multidisciplinary Sci., Göttingen, Germany; [2]Univ. of Göttingen, Göttingen, Germany; [3]Univ. of Oldenburg, Oldenburg, Germany

Abstract: The large diversity of behaviors even among closely related species indicates the evolvability of the underlying neural circuit. At the same time, the behaviors must be functionally robust, but how systems can be both robust and evolvable is still an open question in neuroscience and evolution. Studying robustness and evolvability requires the mapping between genotypes and phenotypes, which is challenging to obtain experimentally. However, models of neural circuits that generate behavior can be used as a proxy of the biological system, and the mapping between model parameters and output can serve as a proxy for the genotype-phenotype map. Here, we combine Bayesian inference and information theory to quantify robustness and evolvability in circuit models. We test this method using a model of the acoustic pattern recognition circuit in crickets. This circuit consists of linear filters and nonlinearities and can reproduce the full behavioral diversity of song recognition found in crickets. We demonstrate that this method correctly obtains the mapping from the model parameters to the diverse recognition behaviors and quantifies the model's evolvability and robustness. The method also identifies directions of sloppiness and stiffness and illustrates how the properties of the parameter map could shape circuit evolution. This approach of characterizing the robustness and evolvability in neural circuit models is applicable to a wide variety of models and systems.

Disclosures: D. Cho: None. **J. Clemens:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.03/U18

Topic: I.06. Computation, Modeling, and Simulation

Support: Glico social cooperation course 230800000001

Title: Understanding brain's computation through neural networks for the halting problem.

Authors: *Y. TAMORI[1], K. MOGI[2];
[1]The Univ. of Tokyo, Meguro-ku, Japan; [2]Sony Computer Sci. Labs., Shinagawa-Ku, Japan

Abstract: Advancements in artificial intelligence have gained inspirations from research in the neuroscience, in terms of e.g. deep learning (LeCun et al. 2015) and attention (Vaswani et al. 2017). It is an interesting scientific and technological question to ask what the human brain uniquely does computationally, as the computations of AI, including LLM (Open AI 2023), exhibit abilities close to humans. LLM are realized as state-transition processes such as Turing machines (Turing 1936). The exact nature of the advantage of the computations performed by the human brain over those performed by a state-transition machine is not yet clear. It is known that there is no universal machine that can solve the halting problem (Pavlotskaya 1973, Rybalov 2007) of Turing machines, and some studies controversially claim (Penrose 1989) that this is the difference between the human brain and the Turing machine. To date, it has not been shown that the human brain can be treated as a machine that can solve the halting problem. Here we study a neural network of real-valued neural elements in its performance of computations such as transfinite induction (Sommer 1995) with ordinal numbers, including limit ordinal numbers, suggesting the possibility of computational processes which would solve the halting problem of Turing machines. It is also suggested that neural networks using real numbers can execute the proof of Goodstein's theorem (Goodstein 1944) using transfinite induction. Goodstein's theorem is a tangible example of human cognition involving understanding (Raichle 2010) and intuition (Zhang et al. 2017), and would provide a test for the ability of computational system to reproduce human-level cognitive abilities. We discuss the possibility that cognitive processes that require computation beyond the Turing machine might be possible with real-valued neural elements. One possible complication would be that there are cases where the computation of transfinite induction breaks down because the elements of the neural network implementing the computations have a finite value of precision in the computation, necessitating the study of how the ideal neural network can be approximated by networks with increasing precision of real values. Based on this analysis, we discuss directions for brain-inspired computational systems, in augmenting the current artificial intelligence technology. Finally, we explore implications for neuroscience, in relevant fields such as the neural bases of memory (Thompson et al. 1996), intelligence (Roth and Dike 2005), and creativity (Beaty et al. 2014).

Disclosures: Y. Tamori: None. **K. Mogi:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.04/Web Only

Topic: I.06. Computation, Modeling, and Simulation

Title: Creation of a dataset to simulate cytoarchitectonic patterns

Authors: *R. YANG[1], D. PARK[2], A. NAZARAN[3], N. BANGERTER[4], J. J. WISCO[5]; [1]Bioengineering, Univ. of Maryland, Vineland, NJ; [2]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Boston, MA; [3]Brigham Young Univ., Provo, UT; [4]Imperial Col., London, United Kingdom; [5]Anat. and Neurobio., Sch. of Med., Boston, MA

Abstract: The human cerebral cortex consists of a heterogeneous layer of neurons and glial cells that are folded on a macroscopic scale into gyri and sulci. Regions of these folds can be subdivided as cytoarchitectonic areas based on spatial cellular patterns, which have traditionally been demarcated by the eye of an expert neuroanatomist. The accuracy of current MRI mapping techniques used to track development or degeneration of cytoarchitectonic areas is dependent on maps that were not quantitatively validated. Therefore, there is a need for an algorithm that can consistently and reliably demarcate cytoarchitectonic areas from tissue slices. Here we present a dataset of images that simulated controlled cytoarchitectonic lamination patterns of various neuronal sizes, density, and number for the purpose of validating our algorithm. Images representing cytoarchitectonic neurons were generated using MATLAB R2017a. Various binary masks were generated following a different set of conditions that helped simulate the cytoarchitectonic environment. One key component is with the spacing of each neuron. Several images were made with neurons uniformly spaced from the centroid with distance, horizontally and vertically, n. This was further expanded to 2n and 3n to generate variable distances. Another key variable of our study is the size of each individual neuron. Images of neurons arranged uniformly were then generated with varying diameters. From these two variables alone, we were able to generate a number of images with varying orientations that can simulate different cytoarchitectonic structures. A total of 17 binary simulation images were generated following a set of conditions that aims to test neuron cell size, density, and number. A number of different algorithms can be used with this simulation to generate quantitative information with neurons. These algorithms can be trained or tested on generated simulation images as a control test before moving forward to actual experimentation. As a result, we can expect an algorithm to have the potential to demarcate cytoarchitectonic regions from tissue slices quantitatively.

Disclosures: R. Yang: None. **D. Park:** None. **A. Nazaran:** None. **N. Bangerter:** None. **J.J. Wisco:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.05/U19

Topic: I.06. Computation, Modeling, and Simulation

Support: JST Moonshot R&D (JPMJMS2012)
JST CREST (JPMJCR18A5)
JST ERATO (JPMJER1801)

Title: Quantizing Temporal Dynamics: A Transformative VQ-VAE Approach for Generalized Neural Decoding

Authors: *N. MIZUGUCHI[1,3], R. FUKUMA[4], H. KISHIMA[5], T. YANAGISAWA[2];
[1]Dept. of Neurosurg., Osaka Univ., Suita, Japan; [2]Inst. for advanced co-creation studies, Osaka Univ., Suita-Shi, Japan; [3]The Univ. of Tokyo, Meguro, Japan; [4]Dept. of Neurosurg., [5]Osaka Univ. Grad. Sch. of Med., Suita, Japan

Abstract: *Objective:* Recent advances in deep neural networks (DNNs) with representation learning have enhanced the decoding accuracy of electrocorticography (ECoG). However, understanding how this time series can be represented in the latent space of DNNs or what acquired representations contribute to the overall increased accuracy remains challenging. While continuous features such as power spectrum have long been the primary focus for neural decoding of ECoG, features that can be generalized across subjects and diverse brain regions will enable improvements in the decoding accuracy of ECoG or its ability to identify potential biomarkers for specific brain states. Recent Vector-Quantized Variational AutoEncoder (VQ-VAE) applications in time-series analysis support the hypothesis that discrete latent features can quantitatively represent brain signals.In this study, we implemented a modified VQ-VAE with a WaveNet decoder using discrete features from a trained VQ-VAE in conjunction with a linear Support Vector Machine (SVM) for downstream movement classification (Shiraishi et al. (2020)). *Methods*: We trained VQ-VAE using 12 h of ECoG signals in the frontal cortex of seven patients while they were staying in a hospital room without performing any specific tasks. The trained model converted the ECoG signals of 256 or 512 ms into eight discrete values, i.e. codebook size k = 2-2048. Using the trained model, we decoded the motor cortical ECoG signals of 11 different patients while they performed three types of hand movements at the given auditory cues. ECoG signals of -20-500 ms according to the cue were used to decode the type of movement using VQ-VAE and conventional γ / high-γ power features (35-50 Hz, 80-150 Hz). *Results:* With a kernel SVM, the classification accuracy using the proposed features (especially codebook size k was 4 and the input size was 512) was 62.3%±8.7% (mean ± 95% confidence interval), which was comparable to that of the power features (64.2% ± 7.2%). *Conclusions:* Our results demonstrate that neural information of ECoG signals can be represented by a small number of discrete latent feature that are generalized to different subjects and cortical regions.

Disclosures: N. Mizuguchi: A. Employment/Salary (full or part-time):; Osaka University. **R. Fukuma:** None. **H. Kishima:** None. **T. Yanagisawa:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.06/U20

Topic: I.06. Computation, Modeling, and Simulation

Title: Closed-loop control-based deep brain stimulation for desynchronizing E-I networks

Authors: A. V. OLUMUYIWA[1], *G. KUMAR[2];
[1]Chem. and Materials Engin., [2]Chem. and Material Engin., San Jose State Univ., San Jose, CA

Abstract: Introduction. Deep brain stimulation (DBS) has emerged as a potential therapy for disrupting pathological synchronous firing patterns of neurons and restoring healthy oscillations in these disorders when pharmacological interventions fail. However, existing DBS devices require extensive clinical interventions to tune stimulation parameters over the treatment period. In our previous work, we developed a novel forced temporal spike-timing stimulation (FTSTS) protocol capable of desynchronizing excitatory-inhibitory (E-I) networks by harnessing long-term neural plasticity. In this work, we extend our previous work and develop feedback-based closed-loop control algorithms for optimizing the stimulation parameters. **Method.** We considered an E-I network consisting of 400 excitatory and 100 inhibitory neurons. The neurons within different subgroups were synaptically connected with a pre-specified probability. In this work, we only considered E-to-I long-term synaptic plasticity and modeled this using an asymmetric Hebbian-based STDP rule. The E-I network under these conditions showed two distinct dynamical regimes, namely, desynchronized and synchronized regimes based on the average synaptic weight of E-to-I connections. We measured the neuronal synchronization using the Kuramoto order parameter. We considered two protocols for DBS stimulation: the coordinated reset and the FTSTS. Under both protocols, we optimized the pulse amplitude, width, and stimulation frequency by developing and implementing the classical PID controller and a neural network-based optimal Model Predictive Controller. **Results**. Our open-loop computational experiments showed that the E firing rate decreased while the I firing rate increased continuously as the network became more synchronized. Additionally, we found that the decrease in the E firing rate was much smaller than the increase in the I firing rate as the network transitioned from an asynchronous regime to a highly synchronous one. Based on these results, we used E and I firing rates as the feedback signals for designing our closed-loop control algorithms to drive the network to the asynchronous E and I firing rates regime. Interestingly, our closed-loop desynchronization results showed that the closed-loop firing rate trajectory in the E-I plane followed a qualitatively similar trajectory as the open-loop stimulation. Additionally, the closed-loop DBS desynchronized the network much faster than the open-loop DBS. **Conclusion.** In conclusion, we found that the average firing rates of subpopulations in an E-I network provide a meaningful feedback signal to guide the design of closed-loop DBS.

Disclosures: A.V. Olumuyiwa: None. **G. Kumar:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.07/U21

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH T32 Grant HD07475
NSF Grant 2023985

Title: Improving brain-behavior associations in functional connectivity with selection of movie timeframes

Authors: *S. CUTTS, J. TANNER, C. SEGUIN, R. BETZEL, O. SPORNS;
Indiana Univ., Bloomington, IN

Abstract: Individual differences and behavioral relationships with functional connectivity (FC) have been shown to vary over time. Most work on time-varying connectivity examines fMRI scans from a subject at rest, but naturalistic stimuli such as movies provide loosely constrained temporal alignment across individuals. With this, fluctuations in FC with stronger brain-behavior relations can be associated with external stimuli. Here, we optimized the selection of time points within multiple movies to find moments that enhance brain-behavioral correlations in FC across 58 separate behaviors. We used 7T fMRI movie data of 126 healthy subjects from the Human Connectome Project. Participants watched four scan sessions of movie clips and performed a battery of out-of-scanner behavioral assessments. An implementation of the Metropolis-Hastings algorithm and simulated annealing was used to find moments within movies that improved behavioral associations. At each step, selected time points were reconstructed into functional connectivity components (FCc; Cutts et al. 2023; Chumin et al. 2023) across selected movie frames. Timeframe selection was then adjusted based on the magnitude of edgewise brain-behavior correlations of the FCc across subjects. Multiple behaviors showed significantly improved transfer of behavioral associations between training and testing groups compared to initialized timestamps (Fig 1A). Optimizations consistently converged onto similar movie time points over multiple cross validations (Fig 1B). The selection of timeframes and brain-behavior correlation maps differed across behavioral measures but shared similar moments between related behaviors (Fig 1C,D). Optimized timestamps selected moments that improved variability across subjects for each behavior compared to initial timestamps (Fig 1E). This work suggests that behavioral relations in FC are differentially related to select moments during movie-watching.

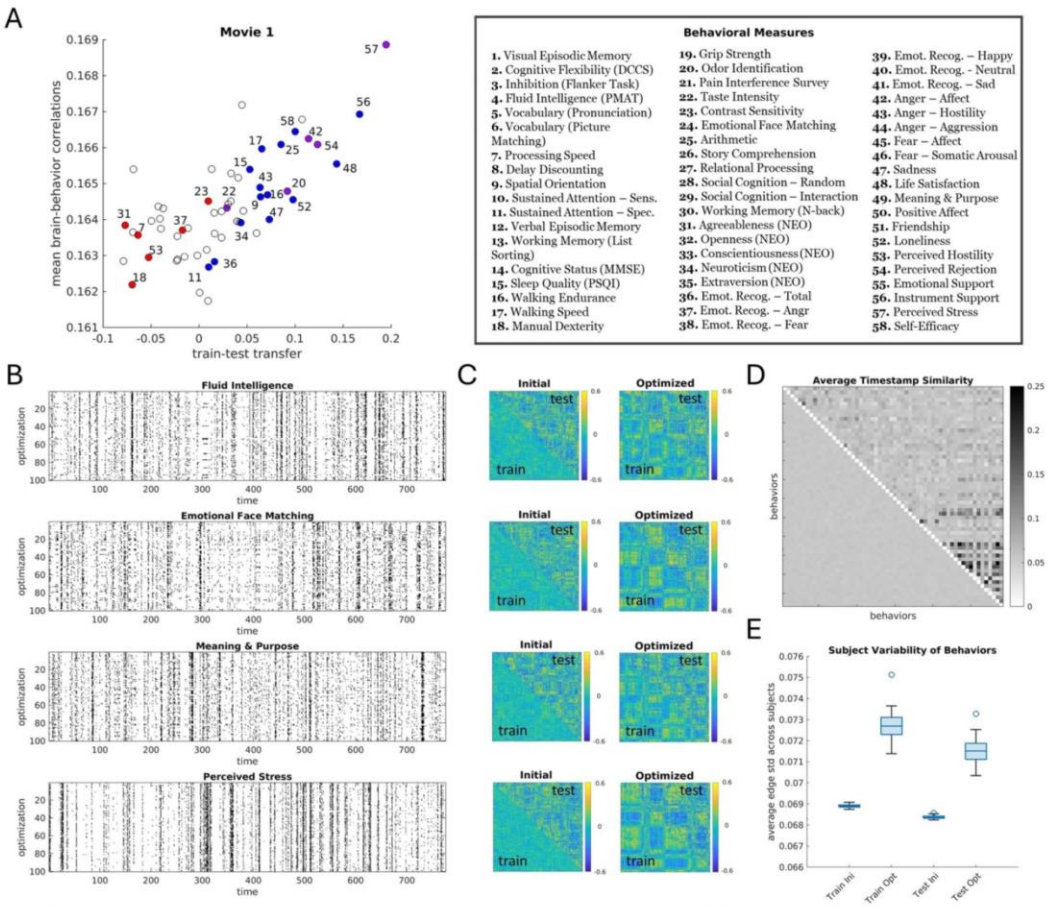

Figure 1. (A) Summary results across all behaviors for movie 1. Functional connectivity components (FCc) were created by computing the agreement of instantaneous bipartitions of the brain regions (Schaefer 200 parcellation) across selected movie frames. Brain-behavior maps were made by correlating each edge of the FCc with behavior and summary measures were computed across all edges and cross validations. Results are shown for optimizations that significantly outperformed initial timestamps ($p<0.05$, FDR) for train-test transfer (blue), magnitude of correlations (red), and both (purple). **(B)** Timestamps optimized for 4 separate example behaviors of movie 1 are displayed. Eighty time points (~10% of each movie) were selected across 100 separate 80/20 (training/testing set) cross validations over the course of 10,000 iterations of simulated annealing optimizations using mean absolute value of brain-behavior correlations as the cost function. **(C)** Brain-behavior correlation maps are displayed for randomly selected initial time points (left) and their corresponding optimized maps (right) of the behaviors directly adjacent in (B). Brain-behavior correlation maps are displayed with an example cross validation from the training set (lower triangle) and results from the held-out testing set (upper triangle). **(D)** Optimized timestamps were compared between each behavior using Jaccard distance and averaged across cross validations for both the initial randomly selected time points (lower triangle) and the optimized (upper triangle). **(E)** Standard deviation across subjects were computed for each edge of the FCc created from the selected time points. Results were averaged across all edges and cross validations separately for each behavior. All behavior values of average standard deviation of FC edges are shown for both training and testing subject groups as well as initial and optimized timestamps.

Disclosures: S. Cutts: None. **J. Tanner:** None. **C. Seguin:** None. **R. Betzel:** None. **O. Sporns:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.08/U22

Topic: I.06. Computation, Modeling, and Simulation

Support: T15LM009451
R00EY028612
R01NS120850

Title: Modeling inter-area communication using multi-task learning artificial neural networks

Authors: *N. GARCIA[1], J. SANTIAGO MORENO[1], D. J. DENMAN[2];
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Abstract: Visual perception is driven by complex computations distributed across diverse populations of neurons. The spatiotemporal coordination of these neurons across populations is not well understood, in part due to practical and technical limitations which make experiments difficult. In this work, we seek to address these limitations by using computational models to explore potential computational strategies in inter-area cortical communication. We trained a multi-task learning convolutional neural network to simultaneously predict spatial frequency, temporal frequency, and angle of short videos consisting of random dot coherence and drifting grating stimuli. Using this network, we quantify how task and stimulus class representations are related in neural activity space and how the network performs readout of upstream activity. Firstly, we demonstrate that the network learns generalized representations that allow linear decoders trained on one stimulus class to predict visual properties of the other stimulus class. Secondly, we show that task-specific branches of the network perform differential readout of shared upstream activity, corresponding to highly orthogonal linear communication subspaces. Lastly, we determine how layers untangle upstream representations. Together, these results provide a multi-task view of linear communication subspaces in artificial neural networks and their role in inter-area communication. Further, they provide a framework for computational hypothesis generation to supplement existing experimental and theoretical efforts. We demonstrate by comparing inter-area communication of upstream activity across stimulus conditions from multi-area Neuropixels recordings.

Disclosures: N. Garcia: None. **J. Santiago Moreno:** None. **D.J. Denman:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.09/U23

Topic: I.06. Computation, Modeling, and Simulation

Support: JHU MINDS Fellowship
NSF NeuroNex Award (Grant No. 2014862)
NSF CAREER Award (Grant No. 1942963)

Title: Why do we have so many excitatory neurons?

Authors: *Q. WANG[1], J. T. VOGELSTEIN[2], C. PRIEBE[3];
[2]Biomed. Engin., [3]Dept. of Applied Mathematics and Statistics, [1]Johns Hopkins Univ., Baltimore, MD

Abstract: How does brain structure support animals' complex behaviors? From Drosophila to humans, the recent development in electron microscopy (EM) connectomes are rendering us access to nanoscale connectomes across various species. Meanwhile, advancements in statistical theory and machine learning are providing insights on functional capabilities of networks. With these, we now have an unprecedented opportunity to investigate the relationship between brain network properties and information processing capabilities of the brains. Functional complexity is a well-established concept in statistical theory and machine learning. Conceptually, it quantifies an agent's ability to perform complex tasks. We designed a measure of functional complexity on networks. Using connectome-based estimates of the connectivity structure in larva Drosophila, we assessed the optimal Excitatory-Inhibitory (EI) ratio that maximizes the functional complexity. Specifically, we built connectome-constrained firing-rate models with the magnitudes of weights given by the synaptic counts in the whole brain connectome, and EI identities randomly assigned.For each EI configuration sampled, we quantified the network's functional complexity. In total, we sampled 8180 different EI configurations. The optimal EI ratio that maximizes functional complexity is 75-81% (percentage of excitatory neurons). Such a range at optimality nicely matches the EI ratio observed across species: ranging from mice and cats, to non-human primates and humans, the EI ratios for neocortex always fall around 80%. Since the EI ratio is conserved across such a wide range of species, it suggests that this is a fundamental principle governing brain anatomy. Our functional complexity measurement provides a normative explanation for this fundamental brain network property. In conclusion, our work systematically investigated what EI ratio leads to maximum functional complexity, establishing a normative framework that links structural properties to their functional significance.

Disclosures: Q. Wang: None. **J.T. Vogelstein:** None. **C. Priebe:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.10/U24

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant No. R01EB029271

Title: Assessment of the Safety of Electrical Stimulation of Peripheral Nerves through Computational Modeling

Authors: *J. DU[1,2], A. W. MORALES[3], J.-M. C. BOUTEILLER[3], G. LAZZI[2];
[2]Electrical Engin., [3]Biomed. Engin., [1]USC, Los Angeles, CA

Abstract: Peripheral Nerve Stimulation (PNS) is a widely established neurostimulation technique used for several medical conditions, including motor function recovery, chronic pain relief, spinal cord injury pain management, and treatment of complex regional pain syndrome. Despite the advent of numerous neural stimulation devices, defining safe electrical stimulation limits on peripheral nerves is still under debate. Establishing clear safety guidelines is crucial for optimizing patient outcomes and advancing neuroprosthetic system research and development. We have developed computational models that depict the impact of electrical stimulation on peripheral nerves. These models are highly detailed and accurate, having been constructed utilizing high-performance computing and machine learning algorithms, including image segmentation through the application of convolutional neural networks (CNN) to ensure anatomical precision. These models are employed to evaluate the safety of the stimulation and to examine potential damage to the nerves. By utilizing the multiscale Admittance Method, combined with detailed 3D models of nerves, we aim to understand how electrical stimulation affects peripheral nerves. The simulated 3D models can precisely predict how electric currents flow through the nerves and allow us to accurately evaluate the level of damage caused by the stimulation. To address the computational demands of these models, we have implemented techniques such as an adaptive meshing algorithm and a parallel Python Admittance Method solver (PAM). The comparison and correlation of experimental data with the results of our computational models will aid in the analysis of factors such as current amplitude and electrode position on the extent of tissue damage. This study outlines our multiscale computational modeling approach and simulation findings. We also discuss the PAM platform's role in simulating current flow within these models. Our results include simulation data and an analysis of experimental data examining nerve fiber changes under various stimulation levels. We found a correlation between experimental data and model predictions at identical stimulation intensities. Future work involves collecting more data to develop comprehensive, robust safety guidelines for electrical neural stimulation, contributing to the creation of safer, more effective neuroprosthetic systems.

Disclosures: J. Du: None. **A.W. Morales:** None. **J.C. Bouteiller:** None. **G. Lazzi:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.11/U25

Topic: I.06. Computation, Modeling, and Simulation

Support: NIMH109548

Title: Spontaneous collective oscillation is seen in networks with Hodgkin-Huxley neurons, but not with generalized leaky integrate and fire neurons

Authors: *A. SHEREMET[1], S. ITO[2], J. DAVIS[1], Y. QIN[3];
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Abstract: Understanding the relation between the properties of the individual neurons and resulting collective behavior is important for guiding us in selecting the right model. Previously, we have found a largely dismissed type of oscillations, where populations of excitatory Hodgkin-Huxley (HH) neurons exhibit collective oscillations when excited by a Poisson-distributed stationary spike input. Interestingly, this behavior is not universal across various simplified neural models. For example, networks with the Generalized Leaky Integrate and Fire (GLIF) neurons fail to show a similar response. The origin of this discrepancy, and its consequences on the dynamics of large neural populations, are not well understood.
In this study, we investigated the dynamical properties of neural populations modeled with the HH and GLIF point neuron models, with the goal of identifying the dynamical elements responsible for this behavior. We conduct a comparative analysis of the theoretical properties of the neurons, to identify the differences in their major dynamical characteristics. We also establish equivalent domains of their respective parameter spaces, as a basis for comparing their dynamics.
The population response to forcing input is further investigated numerically, using the Brain Modeling ToolKit (BMTK) with the NEST simulator. The neural population is forced by spike trains, either stationary or modulated at a low frequency (theta range), distributed randomly across the population. Our simulations suggest that the HH "susceptibility" parameter "h" plays an important role in creating collective oscillations, potentially pointing toward identifying a broad class of neurons that can exhibit such spontaneous oscillations.
Our work highlights potential mechanisms underlying different origins of the oscillatory activity in neural networks. It also emphasizes the importance of model selection for accurately representing specific types of oscillatory activity. This is particularly important for studies on oscillatory properties of the neural network, especially for realistic representation of interaction of oscillations in multiple frequencies (cross-frequency coupling).

Disclosures: A. Sheremet: None. **S. Ito:** None. **J. Davis:** None. **Y. Qin:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.12/U26

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant T32MH065214

Title: The attention schema theory in machine learning: training agents to classify the attention patterns of others

Authors: *K. T. FARRELL, K. ZIMAN, M. S. GRAZIANO;
Princeton Univ., Princeton, NJ

Abstract: The Attention Schema Theory (AST) posits that the human brain maintains a predictive model of its own attention. According to the theory, this attention-modeling machinery may also allow us to predict the attention of others, contributing to social cognition and making us particularly attuned to the patterns of attention in our surrounding environment. While many behavioral and neural findings align with the predictions of AST, there is also supporting evidence accumulating in the domain of neural networks. For example, network architectures that implement AST-inspired attention mechanisms have been linked to increased success in cooperative Multi-Agent Reinforcement Learning tasks. However, a further investigation into the specific advantages obtained by AST-based neural networks is necessary to relate these findings to cognitive theory: is their enhanced performance directly related to an enhanced ability to predict the attentional states of others, rather than general improvements in their nonsocial processing abilities? Here, we present a proof-of-concept showing that while AST-based networks attain no advantage over similar model architectures in general image classification tasks, they significantly outperform other models in the classification of true and spatially-scrambled representations of neural network attentional output. These results suggest that networks designed using the principles of AST are able to better recognize the statistical patterns of attention that are similar to their own, likely contributing to their capacity for behavioral prediction and heightened cooperative abilities in multi-agent contexts.

Disclosures: K.T. Farrell: None. **K. Ziman:** None. **M.S. Graziano:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.13/U27

Topic: I.06. Computation, Modeling, and Simulation

Support: Grant MH118928
Grant DA056394
Grant MH132642

Title: Uncovering Computational Mechanisms of Cognitive Thalamocortical Circuits in Regulating Task Uncertainties

Authors: *X. ZHANG[1], Z. CHEN[2];
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Abstract: Successful execution of complex and flexible decision-making tasks requires identification and processing of multiple sources of uncertainty. Task uncertainty may appear in the form of corrupted or incongruent sensory cues (“cueing uncertainty”), the mapping onto

abstract or behavioral variables (“cue-to-rule mapping uncertainty”), or their likelihood of resulting in reward (“outcome uncertainty”). Dealing with uncertainty such as resolving conflicts and switching tasks is an important component of cognitive control. The cognitive thalamus, involving the higher-order thalamic nuclei such as mediodorsal (MD) thalamus and pulvinar, are believed to play a critical role in this cognitive process in partnership with the prefrontal cortex (PFC). To understand the computational mechanisms of cognitive thalamocortical circuits to enable cognitive control and flexibility, we trained biologically constrained rate-based recurrent neural networks (RNNs) that mimic genetically identified thalamocortical pathways and cell types in the mouse MD-PFC circuit to perform various types of decision-making tasks with three sources of task uncertainties. We present emergent properties of the performance-optimized computational MD-PFC model in a task-dependent manner, including unit tuning, population dynamics, and subspace analysis with respect to task uncertainty variables. Our results support the critical role of cognitive thalamus in information integration, selective regulation, and cortical state control. Our models provide computational insight into bidirectional thalamocortical communications that enable cognitive flexibility as well as dysfunctional cognitive thalamocortical networks underlying psychiatric diseases such as schizophrenia and ADHD.

Disclosures: X. zhang: None. **Z. Chen:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.14/U28

Topic: I.06. Computation, Modeling, and Simulation

Title: Computational modeling of brain network dynamics

Authors: *L. HOHEISEL[1,2], S. DAUN[1,3], J. KAMBEITZ[4,5];
[1]Inst. of Neurosci. and Med. (INM-3), Forschungszentrum Jülich, Jülich, Germany; [2]Department of Psychiatry and Psychotherapy, University Hospital of Cologne, Cologne, Germany; [3]Institute for Zoology, University of Cologne, Cologne, Germany; [4]Dept. of Psychiatry and Psychotherapy, Univ. Hosp. of Cologne, Cologne, Germany; [5]Institute of Neuroscience and Medicine (INM-3), Forschungszentrum Jülich, Jülich, Germany

Abstract: Computational modelling enables us to study brain mechanisms in health and disease. Using simulations, we can explore the brain non-invasively and even perform targeted manipulations. Most current literature models empirical time-averaged functional connectivity (FC), but recent studies show that individuals also express unique dynamic FC profiles. Optimising models to simulate dynamic, rather than just static FC (sFC) enables us to investigate neurobiological correlates of brain network dynamics.
In this study, we used diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (fMRI) data of 200 healthy individuals from the Human Connectome

Project‘s Young Adult dataset, preprocessed by Domhof et al. [1]. We used The Virtual Brain toolbox [2] to perform simulations based on a group-average structural connectome, and four model parameters: i) G, a global coupling scaling parameter, ii) J_i, the local inhibitory synaptic coupling, iii) J_NMDA, the excitatory synaptic coupling, and iv) w_p, the local excitatory recurrence weight. We determined model fits according to four metrics: a) the sFC, b) the FC variance, c) the temporal correlation (TC), and d) the node cohesion (NC). We identified the optimal model for each subject based on both sFC and TC, computed the correlations of parameters and fits of the optimal model with sFC and TC features, and attempted to predict parameters and fits based on sFC or TC features. We used a group-average perturbation approach to investigate the effect of G in each region on overall network connectivity.
The models were able to replicate empirical sFC and TC, but not the FC variance or NC. Fits and parameters exhibited strong associations with brain connectivity. G correlated positively and J_NMDA negatively with a range of static and dynamic FC features ($|r| > 0.3$, $p(FDR) < 0.05$). The TC and sFC fits could be predicted from TC and sFC features respectively ($R^2 > 0.5$). The sFC fit was most affected by coupling alterations in the left paracentral gyrus ($\Delta r = 0.07$), the TC fit by the left pars triangularis ($\Delta r = 0.24$).
Our findings indicate that variability in both static and dynamic FC relates to individual neurobiological characteristics, and that, across subjects, a small number of largely frontal regions drives brain network connectivity. We show that the modeling approach is able to reproduce some dynamic aspects of FC, and that models considering dynamic FC can elucidate the origins of brain network dynamics.
[1] Domhof et al. (2021). Parcellation-induced variation of empirical and simulated brain connectomes at group and subject levels. *Network Neuroscience*
[2] www.thevirtualbrain.org

Disclosures: L. Hoheisel: None. **S. Daun:** None. **J. Kambeitz:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.15/U29

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI No.20H00123

Title: Relationship between fluctuation of spontaneous neural dynamics and the learning in input/output association tasks.

Authors: *T. KURIKAWA;
Future Univ. of Hakodate, Hakodate, Japan

Abstract: Spontaneous neural activity correlates with learning performance, especially with learning speed. For example, brain-computer interface (BCI) technology has shown that when a

target to be learned is more highly correlated with spontaneous activity, the speed at which that target is learned is faster. However, the relationship between spontaneous dynamics and learning speed remains unclear. In this study, we have derived the general relationship between spontaneous activity and learning speed by using the statistical physics approach, the fluctuation-response relationship, in which the response to the external input is determined by the fluctuation of spontaneous activity without the input. We derived the formula that the fluctuation of the spontaneous dynamics determines the learning rate, i.e. the rate of change of the neuronal state through synaptic plasticity. We have also numerically validated this relationship in two specific network models: a random matrix connectivity model and a network model with pre-embedded patterns, such as the Hopfield network, before learning. As a specific case of this relationship, we can reproduce the previous BCI observations. Our results provide a general mechanism underlying the relationship between spontaneous dynamics and the learning process.

Disclosures: T. Kurikawa: None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.16/U30

Topic: I.06. Computation, Modeling, and Simulation

Support: The Sasakawa Scientific Research Grant
Naito Foundation

Title: Development of a lightweight and customizable biophysical neuron simulator

Authors: *K. AKIRA-TAMURA[1], M. IURA[2], R. KURIYAMA[3], T. KOBAYASHI[4], J. IGARASHI[5], T. YAMAZAKI[2];
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Abstract: Computer simulation of biophysical neuron models and their network models enable us to investigate computational principles and capability of neurons that harness morphology of dendrites and nonlinearity of ion channel dynamics. For this purpose, sophisticated modeling tools and efficient simulators are necessary. Moreover, it would be ideal if such tools and simulators were integrated and standardized for existing databases.
The Brain Modeling ToolKit (BMTK), developed by the Allen Institute for Brain Science, is a Python package for such biophysical modeling and simulation, whereas the NEURON simulator is used for simulation as its backend system. Because biophysical simulation requires complex numerical processing, the simulation software can become comprehensive and overwhelming. On the other hand, due to the complexity and the huge codebase, it is quite difficult to modify or

extend the software itself to add new functions and exploit internal parameters. Indeed, porting and optimizing the software to a new computer architecture such as a supercomputer is actually a challenging task.
In this study, we developed a biophysical neuron simulator. The simulator consists of two parts. The first part is a Python module that can be used together with BMTK. The module called "bionet_lite" reads a BMTK script, and generates configuration files that describe neuron populations and synaptic connections across neurons. The second part is a lightweight simulation program that reads those configuration files and performs numerical calculations. The simulation code called "neulite", written in C17, has a clean data structure and is easily customizable by writing codes in C17 directly. For example, it is straightforward to support parallel computing using Message Passing Interface (MPI). So far, our simulator has been able to replicate tutorials 1 to 4 of BMTK, covering a current-clamp single neuron simulation and a balanced network model simulation. Support of MPI was added to the simulator, and now the simulator can be compiled and executed on the supercomputer Fugaku, which is the national flagship supercomputer in Japan. Currently, we are working on the detailed column model of the primary visual cortex reported previously.
In summary, our simulator will provide a means for powerful biophysical modeling owing to BMTK, and flexible simulation owing to the lightweight implementation of the simulator code.

Disclosures: K. Akira-Tamura: None. **M. Iura:** None. **R. Kuriyama:** None. **T. Kobayashi:** None. **J. Igarashi:** None. **T. Yamazaki:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.17/U31

Topic: I.06. Computation, Modeling, and Simulation

Title: Computational simulation for the mechanism of torque-based magnetoelectric neuromodulation

Authors: *G. TSENG[1,2], P.-H. CHIANG[3];
[1]Inst. of Biomed. Engin., Hsinchu City, Taiwan; [2]National Yang Ming Chiao Tung University, Hsinchu City, Taiwan; [3]Natl. Yang Ming Chiao Tung Univ., Hsinchu City, Taiwan

Abstract: Deep brain stimulation (DBS) is widely used to treat brain disorders such as Parkinson's disease, epilepsy, and dystonia. However, the implantation of hardware electrodes in conventional DBS is prone to causing infections, inflammation, and injuries due to micromotion during daily activities. Therefore, various wireless deep brain stimulation methods have been developed to minimize the damage caused by the implantation of conventional DBS. Among all wireless deep brain stimulation technologies, Magnetic-driven Torque-Induced Electrical Stimulation (MagTIES) is the only approach that can trigger neuronal activity with millisecond-scale temporal precision, allowing for the fine-tuning of brain oscillations to specific frequencies.

Unlike magnetostriction-based magnetoelectric stimulation, the mechanism of torque-based magnetoelectric stimulation, such as MagTIES, is not well understood. To investigate the underlying mechanism of this technology, we first demonstrated the magnetoelectric response of MagTIES by measuring the magnetic field-induced electrical responses mediated by magnetic nanomaterials. Next, a detailed simulation of MagTIES using COMSOL Multiphysics was conducted to demonstrate the underlying mechanisms. In the computational modeling, we demonstrated that the magnetic-driven torque, generated by applying a weak alternating magnetic field to a magnetite nanodisc, could induce stress and a piezoelectric response in BaTiO3 nanoparticles, which can produce a sufficient electric field for neuronal stimulation. Finally, we showed that the electric field released from BTO is capable of triggering an action potential in a model neuron. In conclusion, this study elucidates the mechanism of MagTIES and enhances our understanding of its functionality. These results can be leveraged to improve the efficiency of MagTIES, advancing its potential applications in both basic and translational research.

Disclosures: G. Tseng: None. **P. Chiang:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.18/U32

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF DBI 2015317

Title: Tools for the design, simulation, and optimization of synthetic nervous systems

Authors: *W. NOURSE[1], R. D. QUINN[2];
[1]Electrical, Computer, and Systems Engin., Case Western Reserve Univ., Cleveland, OH;
[2]Mechanical Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: A common goal of neuroscience and robotics research is to understand how systems of varying intelligence interact with their environment to generate adaptive behavior. Through implementing models of nervous systems which can interact with an external environment in either simulation or robotic hardware, neuroscientists can validate their models and run experimental studies not possible in animals and roboticists can work towards understanding how intelligent behavior can emerge from some relatively small nervous systems in animals. For this synergy of interests to occur, it is vital to have software which can take a biologically-inspired neural network, also known as a synthetic nervous system (SNS), and run that network in a closed loop with a robotic system. While there is a wide variety of neural simulation software available today, most do not offer an easy path to interface the neural simulation with external systems such as robots or physics engines. Other frameworks which can interface more easily with external systems exist, but either reduce the complexity of neural dynamics or suffer

performance issues when scaling to large networks.
In this work, we present our companion software systems SNS-Toolbox and SNSTorch. SNS-Toolbox is an open-source framework for designing and simulating networks of bio-plausible neurons and synapses at moderate network scale with arbitrary connectivity. We present benchmarking results of SNS-Toolbox against other comparable simulators and showcase some application examples. We also introduce SNSTorch, a companion package to SNS-Toolbox which supports larger networks and layer-based design. We benchmark the speed performance of SNSTorch against SNS-Toolbox on a population-based task, and then demonstrate the optimization of SNS networks on both regression and classification tasks.

Disclosures: W. Nourse: None. **R.D. Quinn:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.19/U33

Topic: I.06. Computation, Modeling, and Simulation

Title: Asymmetric connectivity and cell-type diversity for understanding the cortical dynamics

Authors: *U.-U. NARANTSATSRALT[1], P. EKELMANS[2], N. KRAYNYUKOVA[1], M. ROYO CANO[3], A. BAST[3], M. OBERLAENDER[3], T. TCHUMATCHENKO[1];
[1]Inst. of Exptl. Epileptology and Cognition Res., Univ. of Bonn Med. Ctr., Bonn, Germany; [2]FIAS - Frankfurt Inst. for Advanced Studies, Frankfurt am Main, Germany; [3]In Silico Brain Sci., Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany

Abstract: Cortical circuits have multiple excitatory and inhibitory cell types with cell-type-specific connectivity. How the details of connectivity such as reciprocity, amplitude and relative relation to each other give rise to the observed differences in the firing rate dynamics of the individual cell types is an open question. To address this question, we employed a computational framework incorporating multiple inhibitory or excitatory cell types to help interpret the role of connectivity asymmetries for cortical network dynamics in the barrel cortex. We derived analytical predictions using the stabilized supralinear network (SSN) rate model, confirmed these using the corresponding spiking networks of leaky-integrate-and-fire (LIF) neurons with biologically constrained parameters and compared them to experimental data recorded in the barrel cortex in PT and IT cells. We found that the SSN rate model and LIF network activity were consistent with each other and gave rise to firing rate asymmetries observed experimentally. We derived distinct predictions for the firing rate of the excitatory and inhibitory populations as a function of connectivity asymmetries and considered the influence of the firing rate regime corresponding to the symmetric connectivity set-point. We found that the excitatory asymmetric connectivity did not affect the silencing threshold for firing but could strongly affect the width of the bistable window when the network entered the bistable regime. Conversely, inhibitory asymmetric connectivity could alter significantly the silencing threshold but had only

a weak effect on the bistable window. In conclusion, our study demonstrates that even small cell-type-specific asymmetries in connectivity can give rise to significantly different firing rates across cell types. Furthermore, our findings underline the distinct role of the excitatory and the inhibitory connectivity asymmetries on network dynamics. Our predictions can inform future connectomics experiments and help disentangle cell-type-specific activity patterns and their origin.

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Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.20/U34

Topic: I.06. Computation, Modeling, and Simulation

Support: Laufer Center Director startup funds

Title: Commute times along brain structure better predicts functional connectivities

Authors: *R. RAZBAN, A. BANERJEE, K. DILL, L. R. MUJICA-PARODI, I. BAHAR; Stony Brook Univ., Stony Brook, NY

Abstract: Structure determines function. However, this universal theme in biology has been surprisingly difficult to observe in human brain neuroimaging data. Here, we link structure to function by accounting for signaling dynamics through the commute time: the number of steps for a random walker to go from region A to B and then back to A. Based on white matter tracts from diffusion MRI, commute times have an average ± standard deviation Spearman correlation of -0.26 ± 0.082 with functional MRI functional connectivities across 434 UK Biobank individuals. In comparison to leading communication measures such as search information and communicability, commute time significantly better predicts functional connectivities with Spearman correlations at least 1.5 times larger on average. This difference widens to more than 5 times larger when commute time is correlated to only the top mode of functional connectivity. Our results are supported by simulations of brain function that clearly demonstrate commute time's ability to account for polysynaptic connectivity and better link structure to function.

Disclosures: R. Razban: None. **A. Banerjee:** None. **K. Dill:** None. **L.R. Mujica-Parodi:** None. **I. Bahar:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.21/U35

Topic: I.06. Computation, Modeling, and Simulation

Title: Zoo of RNNs: A comprehensive analysis of recurrent neural networks trained on synthetic behavioral tasks

Authors: *H. AKENGIN[1], A. CIMEN[2], M. YUKSEKGONUL[3], A. S. ALEXANDER[5], F. DINC[4];
[1]Computer Sci., [2]Electrical and Electronics Engin., Ozyegin Univ., Istanbul, Turkey; [3]Computer Sci., Stanford Univ., Palo Alto, CA; [4]Applied Physics, Stanford Univ., Stanford, CA; [5]Psychological and Brain Sci., UC Santa Barbara, Santa Barbara, CA

Abstract: System neuroscientists regularly investigate cognitive functions by studying model animals through predefined behavioral tasks in controlled laboratory environments. To extend this study to neural mechanisms in silico, the advent of artificial intelligence research has enabled the exploration of neural computation strategies within artificially trained neural networks on similar synthetic behavioral tasks. However, these synthetic tasks lack systematic evaluation and are often non-standardized and fragmented across several prior works. To address this issue, we introduce a comprehensive benchmark of standardized behavioral tasks, on which we train recurrent neural network (RNN) models. To dissect the computational strategies employed by RNNs, we utilize the recently developed latent circuit theory, which effectively maps the computations of high-dimensional RNN units onto an interpretable low-dimensional dynamical system, i.e., the latent circuit. Building on this framework, we quantify the complexities of various tasks and establish a mechanistic equivalence between two widely used RNN models in systems neuroscience, further enhancing our understanding of their functional capabilities. To facilitate future extensions of the benchmark and support ongoing research in this field, we outline detailed methodologies for standardizing these tasks and offer a publicly accessible codebase. Our findings lay a standardized and principled foundation, paving the way for future comparative studies of neural computation in systems neuroscience.

Disclosures: H. Akengin: None. **A. Cimen:** None. **M. Yuksekgonul:** None. **A.S. Alexander:** None. **F. Dinc:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.22/V1

Topic: I.06. Computation, Modeling, and Simulation

Title: Recurrent Neural Networks Utilize Different Mechanisms when Learning Kalman Systems

Authors: *P. JIANG[1], M. AOI[2];
[1]UCSD, LA JOLLA, CA; [2]Neurobio. & Data Sci., UCSD, San Diego, CA

Abstract: Advancement of brain recording technologies augments the number of neurons for long-timescale recording, yet our understanding of neural dynamics remains limited. To fill this gap, recurrent neural networks (RNNs) have served as surrogates for the brain to reproduce animal recordings and conduct math analyses. However, previous studies have shown that substantially different neural networks may yield the similar input/output relationships due to the low dimensional nature of task dynamics. Thus, the use of RNNs to understand the brain begs the question, how do we know if the dynamics learned by an RNN reflects brain dynamics? To address this, we let RNNs learn the input/out mapping of a well characterized, simple system, the Kalman filter. It allows analytically comparing mechanisms and determining properties that are robust or sensitive to model choice, which is hard to realize in more complex systems common in neuroscience studies. We found that RNN dynamics varies dramatically with different activation functions (linear, ReLU, tanh), number of hidden units and regularizations. We investigated dynamics of RNNs by mean squared error (MSE), autocorrelation and reproduction of Kalman gain. Among all RNNs, linear RNNs showed the fastest training and testing errors reduction, while ReLU RNNs with 100 hidden units achieved the lowest MSE. We then compare the mean autocorrelations of Kalman system outputs, and activities and outputs of RNNs reaching MSE<0.003. While the autocorrelations of the Kalman system and RNN output overlay, activity autocorrelations differ a lot. Autocorrelations of linear RNNs overlay with Kalman system, of ReLU RNN decay much slower than its output, while of tanh RNNs show a high variance: 100 hidden unit RNNs almost overlay with its outputs, while 1000 hidden unit RNNs either decay much faster or exhibit oscillation. We then derive formulas to estimate the Kalman gain from RNN weights and hidden units' activities. For weight estimation, only linear RNNs capture the true matrix while ReLU RNNs deviate the most from ground truth. Regularization improves matrix estimation, especially for tanh RNNs, but increases MSEs. Estimation from activity necessitated more principal components than the true system dimension. Our results imply that nonlinear RNNs exhibit different computing mechanisms from linear dynamical systems, while regularization mitigating disparities. We will present analysis using more recent methods that envision network dynamics as living on a manifold to compare/contrast RNN dynamics (eg. dynamical similarity analysis, dynamical model embedding, and neural manifolds).

Disclosures: P. Jiang: None. **M. Aoi:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.23/V2

Topic: I.06. Computation, Modeling, and Simulation

Title: Discovering Symbolic Constraints on Neural Dynamics

Authors: *R. D. KELLER, L. R. LEWIS, X. PITKOW;
Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Almost every natural system can be modeled using the mathematical framework of dynamical systems. Because they provide an explicit, symbolic relationship between input and output dimensions, dynamical systems are amenable to rich analyses that allow us to thoroughly investigate mathematical properties of natural systems. However, the dynamical system that governs real-world data is not always available to the investigator. Unlike measurements taken from well defined natural systems where underlying differential equations emerge from physical laws, such as fluid flow or heat transfer, measurements from complex systems, like networks of spiking neurons in the brain, do not have underlying dynamics with obvious symbolic form. Uncovering the dynamical system of a neural manifold not only allows deeper insights into computational properties of neural dynamics, but it also affords efficient deep learning based neural decoding by leveraging the governing equations of the manifold as an inductive bias in the learning algorithm. Existing methods that model dynamical systems using deep neural networks lack an interpretable input-output relationship. On the other hand, existing methods that do recover an interpretable relationship utilize symbolic regression, which is sensitive to noise and limits dynamics to those defined in terms of explicit functions of the neural state variable. In order to overcome these drawbacks, we propose an inverse Physics-Informed Neural Network (iPINN) model to learn dynamical systems in symbolic form from neural data. Our model recovers a closed form expression for dynamics of neural state variables in terms of differentials rather than explicit functions. This formulation allows us to discover general constraints on dynamics, such as conservation of energy, from neural data. Further, because the model is parameterized by a neural network, robustness to noise emerges naturally through a well-designed training procedure. Ultimately, our model provides a framework to study 1) how neural dynamics encode latent world or task physics, 2) what constraints on neural dynamics emerge from task-driven behavior, and 3) whether dynamical structures that are shared across behaviors and subjects can be leveraged in training and calibrating deep learning based brain-computer-interfaces.

Disclosures: R.D. Keller: None. **L.R. Lewis:** None. **X. Pitkow:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.24/V3

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF 2023R1A2C200621711

Title: Influence of Scale-Free Topology in the Brain Network on Information Processing

Authors: *D. LEE[1], Y. LEE[2], H.-J. PARK[3];
[1]Yonsei Univ. Col. of Med., Seodaemun-gu, Seoul, Korea, Republic of; [2]Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [3]Dept. of Nuclear Med., Yonsei Univ. Col. Med., Seoul, Korea, Republic of

Abstract: The brain possesses a sophisticated modular system and processes information through interconnected modules, contributing to its diverse functions. Many biological experiments and computer simulations have shown that the intricate dynamics of information flow, such as integration and segregation, are closely related to this modular topology. However, despite significant advancements, there remains a notable gap in our understanding of how the connection topology within and between modules influences intricate information processing.
In this study, we explored how the topology of anatomical connections influences information processing in the brain. Initially, we investigated the topology of functional networks in various brain systems, including data from the visual cortex of mice and the tectum of zebrafish. We found that the modules in these systems are interconnected with a scale-free topology functional network, displaying dynamic fluctuations in brain activity that contribute to information integration and segregation. Using computational modeling, we simulated neuronal dynamics based on scale-free structural connectivity to examine how the characteristics of topology shape functional networks and influence information processing. To efficiently simulate the activity of thousands of neurons, we developed parallel GPU-based code, utilizing the Izhikevich neuron model for large-scale spiking neural network simulations. We observed how spiking patterns were segregated and integrated under various topologies. The results revealed that in random networks, integration within modules was low, and segregation between modules was not particularly high. However, in the scale-free network, both integration and segregation values maintained a high level. Additionally, the core-peripheral connection between modules exhibited a higher dynamic fluctuation compared to the core-core connection within modules.
Furthermore, using a large-scale model with whole zebrafish brain structural connection data, which exhibits scale-free network properties within modules, we simulated the information flow and dynamic fluctuation in the zebrafish brain, similar to empirical zebrafish calcium imaging data.
In conclusion, our study underscores that the connectivity properties of the scale-free topology at the individual neuron level play a significant role in shaping brain information processing.

Disclosures: D. Lee: None. **Y. Lee:** None. **H. Park:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

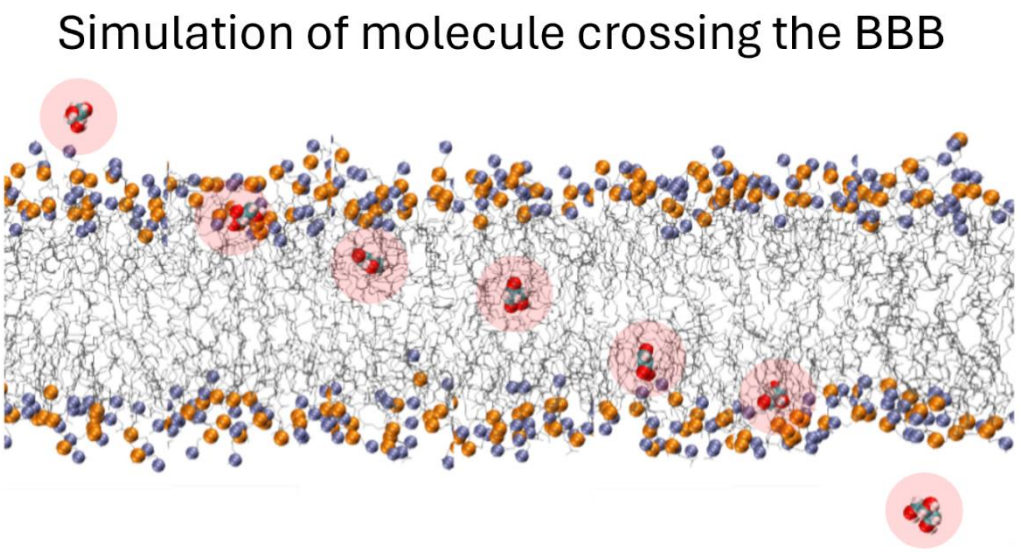
Program #/Poster #: PSTR145.25/V4

Topic: I.06. Computation, Modeling, and Simulation

Title: Optimising the kinetic profile of CNS drugs through novel computational screening methods

Authors: *N. A. BERGLUND;
Kvantify, Copenhagen, Denmark

Abstract: The quest to develop efficacious drugs for neurological conditions is fraught with complexities, primarily due to the intricate nature of the brain and the formidable blood-brain barrier (BBB). Traditional methods of drug discovery are often slow and costly, with a high attrition rate in the clinical phases. Recognizing these challenges, Kvantify, in collaboration with King's College London, has pioneered innovative computational techniques to predict the kinetic properties of small molecules, including their unbinding kinetics, which are crucial for assessing the duration of drug efficacy within the brain. These methods also evaluate the potential of compounds to traverse the BBB, a critical step in ensuring therapeutic agents reach their intended targets in the central nervous system. By simulating these properties accurately, Kvantify's approach significantly streamlines the screening process, allowing for the rapid identification of promising compounds. This not only accelerates the pace of neuro drug discovery but also substantially mitigates the risks associated with the development pipeline. The integration of such computational tools holds the promise of transforming the landscape of neuropharmacology, ushering in a new era of targeted, effective treatments for neurological disorders. In this work we report how we deployed these novel computational techniques to rapidly screen candidates targeting kinase receptors linked to Alzheimer's Disease and select high quality candidates to move forward for experimental evaluation.



Disclosures: N.A. Berglund: None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.26/V5

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CAREER 1943467

Title: A reinforcement learning framework for investigating the learning algorithms underlying motor adaptation

Authors: *D. XIAO[1], J. C. KAO[2];
[1]Electical and Computer Engin., UCLA, Los Angeles, CA; [2]Electrical and Computer Engin., UCLA, Los Angeles, CA

Abstract: Recent research characterized changes in preparatory activity of the motor cortex during motor learning. These changes were thought to be neural correlates of motor memory. Notably, during each experiment block, the preparatory activity for each target shifted in a similar direction and distance regardless of proximity to the target that was being trained. The specific geometry of these shifts during learning, unlearning, and relearning blocks were hypothesized to implement the acquisition, retention, and retrieval of motor memories (Sun, O'Shea, et al., Nature 2022). This leads to the question: what learning algorithms lead to the emergence of these phenomena when monkeys perform a curl field (CF) adaptation task?
In order to study this question, we trained recurrent neural network (RNN) models using reinforcement learning (RL) with novel regularization terms to perform realistic reaching trajectories over the course of learning. Popularly, supervised learning with backpropagation through time (BPTT) has been used to train RNN models. Due to BPTT's biological implausibility, the utility of these models is limited to analysis in their frozen state. In order to expand investigation to the learning process, we use a more biologically plausible RL paradigm to train the model.
We find these models, despite lack of supervision, reproduce many behavioral findings from human and monkey CF adaptation experiments. Namely, relearning is faster than initial learning, indicating formation of motor memories. Optimal reaches under a CF are not straight, but rather curved, which has been observed in humans and macaques.
These models also captured many key neurophysiological findings from (Sun, et al., 2022). We found that the model's preparatory activity shifted uniformly, independently of the distance to the CF trained target. Also, the learning shift was orthogonal to the washout shift, replicating the neurophysiological findings.
Additionally, we found that the washout shift becomes more orthogonal to the learning shift when the RNN recurrent weights are frozen after a period of pretraining. This is in line with the observation that, for the time scale of the task blocks in (Sun, et al., 2022), learning likely occurs through modification of activity in the output-null space of the premotor cortex, rather than through connectivity changes within M1.
Together, this work provides a modeling framework that takes a step towards asking interesting yet complex questions about the brain's algorithms during motor learning. These results may inform additional future theoretical exploration of the algorithms underlying motor memory acquisition, retention, and retrieval.

Disclosures: D. Xiao: None. **J.C. Kao:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.27/V6

Topic: I.06. Computation, Modeling, and Simulation

Support: GR5272193

Title: Exploring Multi-Feature In-Context Learning in the Brain, Neural Networks, and Ideal Observers

Authors: *A. RASHED AHMED[1], T. SERRE[2], M. R. NASSAR[3];
[1]Brown Univ. Neurosci. Grad. Program, Providence, RI; [2]Brown Univ., Providence, RI; [3]Metcalf Hall, Brown Univ., Providence, RI

Abstract: Flexible behavior depends critically on recognizing environmental changes and rapidly updating relevant internal representations. However, inferring which internal representations should be updated in high-dimensional real-world environments can be difficult. This is further exacerbated if the state of the environment must be inferred in real-time, thereby making inference updates context-dependent. Here, we explore the computational basis of human flexibility in adapting to environmental cues through a visual predictive inference task called the Bouncing Ball task. Our task involves bouncing ball stimuli with separate color and velocity dimensions that undergo occasional discrete changepoints, the former of which is sometimes occluded. The goal of the task is to predict the ball's color based on prior observations of position and color transitions within the same trial. A key manipulation in the task was parametrically varying two variables that control the degree to which the color changed: The hazard rate determines how likely a color transition is to occur randomly, and the contingency determines how likely it is to occur whenever there is a velocity change, such as on a bounce. For each trial, we sample from two hazard rates (1%, 4%) and three contingencies (10%, 50%, 90%) to give six possible task conditions, requiring in-context learning for optimal performance. In this study, we collect pilot data and investigate the differences in behavioral outcomes between human participants, neural networks, and ideal observer models. We first show that human participants reliably learn the task, exhibiting behavioral sensitivity to all task conditions similar to the ideal observer models. We also find that when the contingency is set to 50%, participants exhibit a bias toward predicting a color transition more often than the ideal observer models. However, when trained on the same task, neural networks fail to exhibit any sensitivity to different hazard rates but do so for different contingencies in an unbiased manner when compared to the ideal observer. We further show that generalized linear models fit to the predictions made by these three groups. These findings implicate qualitative differences in the computational mechanisms leveraged by the brain and neural network models in multidimensional environments which should be further explored.

Disclosures: A. Rashed Ahmed: None. **T. Serre:** None. **M.R. Nassar:** None.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.28/V7

Topic: I.06. Computation, Modeling, and Simulation

Support: chercheurs-boursiers en intelligence artificielle from the Fonds de recherche du Quebec Santé
UNIQUE Excellence Scholarship

Title: Continually inferring behaviorally-relevant structure from complex neural datasets using hypernetworks

Authors: *A. JAMKHANDI[1], O. CODOL[2], M. G. PERICH[3];
[1]Computer Sci., Univ. de Montréal, Montreal, QC, Canada; [2]Univ. de Montreal, Montréal, QC, Canada; [3]Dept. of Neurosci., Univ. de Montréal, Montreal, QC, Canada

Abstract: Brains are remarkably adept at continually adapting their internal states to meet evolving behavioral demands in response to changing stimuli. To that end, brains are capable of compositionally combining aspects of different tasks or knowledge to achieve future goals efficiently. This fluidity of neural representations poses a challenge for our models of neural computation, which often assumes a static view of the statistics of neural responses by leveraging many repeated stimuli. For example, while traditional recurrent neural networks (RNN) have proven to be powerful models of neural circuits, they are best viewed as a static window into a particular neural computation. The brain, in contrast, can flexibly adjust to changing internal or environmental demands to drive complex behaviors. Here, we introduce a new class of data-driven models of neural data that leverages hypernetworks to continually learn the interactions inherent in neural populations of multi-region neural recordings. The hypernetwork models are trained to directly recapitulate the dynamics of neural recordings at single-neuron resolution. Hypernetworks comprise a set of linked neural networks—a feedforward layer and a downstream recurrent layer—that learn dataset-specific embeddings to flexibly set the parameters of the downstream network. While a common method in machine learning to overcome the problem of catastrophic forgetting during continual learning, we posit that they can be positioned as a useful model of top-down control of neural circuits. Using simulated data, we demonstrate that we can capture arbitrarily large and complex datasets in a single, unified model and show that we can extract informative features from both the dataset embedding and the learned downstream recurrent weights. We then apply the method to neural datasets from behaving animals and demonstrate the efficacy of our model in uncovering latent relationships in large, interacting neural populations.

Disclosures: A. Jamkhandi: A. Employment/Salary (full or part-time):; Universite de Montreal, Mila. **O. Codol:** A. Employment/Salary (full or part-time):; Université de Montreal, Mila. **M.G. Perich:** A. Employment/Salary (full or part-time):; Université de Montréal, Mila.

Poster

PSTR145: Network Computation: Theory and Modeling I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR145.29/Web Only

Topic: I.06. Computation, Modeling, and Simulation

Title: Unleashing the Potential: A Paradigm Shift in Reinforcement Learning and Sensory-Motor Integration

Authors: *Y. KYUNG;
Yonsei Univ., Seoul, Korea, Republic of

Abstract: In the vast realm of machine learning, reinforcement learning takes center stage as a prominent and systematic technique, empowering agents to deliberately shape their actions. Through astutely leveraging the agent's responsiveness to the environment, its decision-making prowess evolves gradually. However, the intricate nature of sensory motor mechanisms poses challenges for traditional reinforcement learning models, necessitating a breakthrough. Introducing our pioneering framework, firmly rooted in statistical theory and control theory, we present a transformative solution to overcome these limitations. At its core, our framework introduces a novel perspective—an artfully crafted cost function for selecting actions. This crucial foundation serves as the bedrock for an algorithm that deftly estimates rewards and discount factors, drawing insights from the rich tapestry of biological data. The result is an estimation process that unlocks unparalleled precision, enabling precise predictions of escape behaviors. Inspired by the wonders of neuroscience, our cutting-edge model embraces a strategic approach. By intelligently decomposing complex tasks into independent decision modules, we lay the groundwork for training an artificial agent capable of faithfully emulating the intricacies of biological escaping systems. This strategic orchestration empowers the agent to gracefully navigate its environment, culminating in a symphony of intelligent actions. Embark on a captivating journey where the fusion of reinforcement learning and sensory-motor integration reveals untapped potential. Together, we challenge conventional wisdom, reshape the landscape of artificial intelligence, and unlock new horizons in decision-making capabilities.

Disclosures: Y. Kyung: None.