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Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.01/A1

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NRF-2020R1A5A1019023
NRF-2022R1A2C1004913
RS-2024-00332875
BK21 Four Biomedical Science Program

Title: Senp8 controls synapse development by regulating deneddylation in neurons

Authors: *S. LEE[1], J.-M. SONG[2], M. KANG[2], Y. SUH[2];
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Abstract: Neddylation is a cellular process in which the neural precursor cell expressed, developmentally down-regulated 8 (NEDD8) is conjugated to the lysine residue of target proteins via serial enzymatic cascades. Recently, it has been demonstrated that neddylation is required for synaptic clustering of metabotropic glutamate receptor 7 (mGlu7) and postsynaptic density protein 95 (PSD-95), and the inhibition of neddylation impairs neurite outgrowth and excitatory synaptic maturation. In this study, we hypothesized that deneddylating enzymes can regulate neuronal development by counteracting the process of neddylation. We find that SUMO Peptidase Family Member, NEDD8 Specific (SENP8) acts as a key neuronal deneddylase targeting the global neuronal substrates in primary rat cultured neurons. We demonstrate that SENP8 negatively regulates neurite outgrowth through multiple pathways, including actin dynamics, Wnt/β-catenin signaling, and autophagic processes. Alterations in neurite outgrowth by SENP8 subsequently result in the impairment of excitatory synapse maturation. Our data indicate that SENP8 plays an essential role in neuronal development and is a promising therapeutic target for neurodevelopmental disorders.

Disclosures: S. Lee: None. **J. Song:** None. **M. Kang:** None. **Y. Suh:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.02/A2

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant HD092369

Title: Leptin signaling regulates the activity of specific proteases to promote the development of glutamatergic synapses in the developing hippocampus

Authors: *J. RODRIGUEZ LLAMAS, C. DILLON, G. A. WAYMAN;
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Abstract: Neurotrophic factors direct the development of the nervous system, and impairments in their function lead to neurological disorders. Therefore, understanding how they regulate brain development is of paramount importance. The adipokine leptin, involved in energy balance, exerts neurotrophic effects on the central nervous system. Leptin is also synthesized in the hippocampus, promoting spinogenesis and synaptic plasticity, while rodent models with altered leptin signaling exhibit impairments in these processes and defects in hippocampal-related functions, such as impaired learning and spatial memory. Notably, altered leptin signaling is also associated with mental and cognitive disorders in humans, characterized by changes in dendritic spines. Leptin increases the number of dendritic spines and the frequency of mini excitatory postsynaptic currents in developing hippocampal neurons, evidencing an increase in functional glutamatergic synapses. Since morphological changes in dendritic spines are considered the structural basis of learning and memory, leptin's role in spinogenesis may explain the defects observed in rodent models with impaired leptin signaling. Nonetheless, the molecular mechanisms underlying leptin neurotrophic effects are poorly understood. The endopeptidase matrix metalloproteinase 9 (MMP9), involved in processing extracellular matrix and synaptic components, plays an essential role in spine plasticity in the hippocampus, profoundly influencing learning and memory. We have previously shown that MMP9 and the MMP9 activating-lysosomal protease cathepsin B are crucial for the effects of leptin on dendritic spines in the developing hippocampus and that leptin signaling regulates MMP9 expression, release, and activity in neurons. Here, using a combination of cell and molecular biology, biochemistry, and microscopy approaches, we further investigated the interaction between leptin signaling and these proteases. We found that leptin only requires the gelatinase MMP9 for its neurotrophic effects, as knocking down the gelatinase MMP2 did not prevent leptin-induced increase in mushroom spines on cultured hippocampal neurons. We also explored whether leptin could promote MMP9 mRNA trafficking to the dendritic spines, thus facilitating MMP9 release in the perisynaptic space. Finally, we showed that leptin promoted the exocytosis of cathepsin B-containing vesicles, thereby increasing cathepsin B release. Thus, our results indicate that leptin regulates the activity of a small group of proteases, ensuring precise control of the neurotrophic effects of leptin in the developing hippocampus.

Disclosures: J. Rodriguez Llamas: None. **C. Dillon:** None. **G.A. Wayman:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.03/A3

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: National Brain Research Centre Core Fund
Department of Biotechnology Government of India

Title: Synapse enriched long non-coding RNA regulates inhibitory synapse development

Authors: K. GARG[1], B. SRINIVASAN[2], S. SAMADDAR[1], ***S. BANERJEE**[1];
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Abstract: Synapse formation in hippocampus has been shown to be regulated by various transcriptional control. Although, RNA-based mechanism of glutamatergic synapse development gained an attention, our understanding of inhibitory synapse development involving regulatory RNA remains elusive. More recently, our transcriptomic analysis identified a set of synapse-enriched long non-coding RNAs (lncRNAs). An expression profile during the window of synapse development identified a subset of lncRNAs that showed an exponential increase in expression during this period. Prompted by these observations, we hypothesized that lncRNAs could regulate synapse development. We have analysed the excitatory and inhibitory synapse density in hippocampus *in vivo* following knockdown of two key lncRNAs based on their peak expression during synapse formation. We observed that the knockdown of NO1Rik, but not Zfas1, in embryonic CA1 neurons reduces inhibitory synapse density without influencing excitatory synapse formation. The knockdown of NO1Rik in CA1 neurons showed a significant reduction of both perisomatic and dendritic inhibitory synapse density. We have measured synaptic activity using whole-cell patch clamp recordings from hippocampal neurons following knockdown of NO1Rik. Our patch clamp data showed a significant reduction in amplitude, but not frequency, of miniature inhibitory post-synaptic current (mIPSC). Consistent with our observations from synapse density analysis, we observed that the knockdown of NO1Rik has no effect on miniature excitatory post-synaptic current (mEPSC). RNA-Seq analysis from CA1 following loss of NO1Rik function detected 206 downregulated and 65 upregulated protein coding transcripts. The Gene Ontology (GO) analysis of downregulated transcripts revealed an enrichment of GO-terms that includes cilium movement, motile cilium, transporter complex and ion channel complex. More recently, cilium function has been attributed to excitatory synapse development. Prompted by this data, experiments are in progress to visualize how lncRNA activity governs inhibitory synapse development involving the functions of cilia. Comprehensively, our study will provide a detailed non-coding RNA based molecular framework that is necessary for inhibitory synapse development in hippocampus.

Disclosures: K. Garg: None. **B. Srinivasan:** None. **S. Samaddar:** None. **S. Banerjee:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.04/A4

Topic: A.06. Synaptogenesis and Activity-Dependent Development

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ERC grant ERC-ST2019 850769
Eccellenza Grant PCEGP3_194220

Title: Nmda receptor-dependent synapse formation in the hippocampus

Authors: *N. LEIBOLD[1], N. F. HIGGS[1], S. KANDLER[2], A. KHAN[1], F. DONATO[2], L. C. ANDREAE[1];
[1]Ctr. for Developmental Neurobio., King's Col. London, London, United Kingdom; [2]Biozentrum, Univ. of Basel, Basel, Switzerland

Abstract: While neuronal activity is important for synapse refinement and maintenance, its contribution to synapse formation and dendritic arborization remains unclear. Our previous work in dissociated hippocampal neurons identified a timeframe prior to the establishment of synapses during which spontaneous glutamate release facilitates the branching of dissociated hippocampal neurons by targeting NMDA receptors (NMDARs). We now demonstrate the role of NMDARs in synapse formation and dendritic maturation in hippocampal CA1 pyramidal neurons in cultured slices and *in vivo*. To test whether NMDARs guide synapse formation during development, we pharmacologically blocked NMDARs at different timings in organotypic slices. Blocking NMDARs during late embryonic development reduced Schaffer collateral synapse densities in CA1, while no effects were seen following postnatal perturbation. In order to sparsely block NMDAR function during early development *in vivo*, we performed in utero injections of AAVs expressing Cre and a flexed reporter in transgenic mice with a conditional deletion of the obligatory GluN1 subunit. We confirmed complete loss of NMDAR function in CA1 pyramidal neurons using whole-cell patch-clamp electrophysiology. Similar to the results in organotypic slices, we observed effects on excitatory synapse densities and dendritic morphology. Using timelapse *in vivo* structural imaging we noticed that cells expressing NMDARs exhibited more dynamic dendritic arbors. *In vivo* functional imaging further revealed that NMDARs are frequently activated and give rise to minute-long dendritic calcium transients which correlate with the emergence of branching filopodia. Overall, our results shed light on the developmental role of NMDARs during synaptogenesis and dendritic arborization.

Disclosures: N. Leibold: None. **N.F. Higgs:** None. **S. Kandler:** None. **A. Khan:** None. **F. Donato:** None. **L.C. Andreae:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.05/A5

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: R00-MH117235
Alfred Sloan Foundation Sloan Fellowship in Neuroscience

Title: Adhesion GPCRs converge on Gα12/13 signaling to establish hippocampal PV inhibitory circuits

Authors: K. A. GARBETT[1,2], ***B. TOSUN**[1,2], C. M. SMITH[1,2], R. SANDO[1,2];
[1]Pharmacol., Vanderbilt Univ., Nashville, TN; [2]Vanderbilt Brain Inst., Nashville, TN

Abstract: The process of synapse formation involves multiple complex stages and synaptic adhesion molecules play important roles in organizing synaptic junctions. Specifically, one group of adhesion proteins, adhesion G-protein coupled receptors (aGPCRs), mediate cell-cell adhesion with its extracellular adhesive domains and initiate intracellular signaling cascade with its seven transmembrane (7TM) GPCR domain. Recent studies suggest that adhesion GPCRs have a role in different aspects of synaptic organization to shape hippocampal circuits. In this study, we investigated the G protein coupling of aGPCRs and we found that the Gα12/13 pathway lies downstream of 2 families of adhesion GPCR receptors (LPHNs and BAI). These results highlighted the limited comprehension of the roles of the Gα12/13 pathway at the synapses in the postnatal brain. To fill this gap, we performed whole-cell patch clamp electrophysiology and determined the functional roles of the Gα12/13 pathway *in vitro*. Whole-cell recordings identified Gα12/13 pathway is critically important for inhibitory synapse formation *in vitro*. Compared to the control, Gα12/13 knockdown neurons have significantly reduced miniature inhibitory postsynaptic currents (mIPSCs) amplitude and frequency which were rescued by expression of Gα12 and Gα13 proteins. Next, we delivered shRNA lentiviral vectors into hippocampal CA1 region with bilateral stereotactic injection, and we labeled inhibitory and excitatory synaptic densities with immunohistochemistry. We observed reduced inhibitory synaptic puncta density *in vivo* and we observed presynaptic terminals of parvalbumin interneurons throughout the CA1 region were the most affected. Overall, these results suggest that Gα12/13 signaling shapes inhibitory synapse assembly in a subtype-selective manner, supporting that this pathway is critically important for inhibitory synapse assembly.

Disclosures: K.A. Garbett: None. **B. Tosun:** None. **C.M. Smith:** None. **R. Sando:** None.

Poster

PSTR433: Synapse Dynamics During Development

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Program #/Poster #: PSTR433.06/Web Only

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: KAKENHI 21K07274

Title: Potential roles of immediate early G protein-coupled receptor 3 gene expression during neuronal differentiation

Authors: F. IKAWA, H. SHIRAKI, K. HARADA, I. HIDE, N. SAKAI, ***S. TANAKA**; Hiroshima Univ. Grad. Sch. of Biomed. and Hlth. Sci., Hiroshima, Japan

Abstract: G protein-coupled receptor 3 (GPR3), a member of the class A rhodopsin-type GPCR family, is widely expressed in various neurons (Saeki et al., FEBS 1993; Ikawa et al., Brain Res 2021). GPR3 is unique because it constitutively activates the Gαs protein without a ligand, thereby increasing basal intracellular cAMP levels. Previous research has shown that GPR3 promotes neurite outgrowth (Tanaka et al., JBC 2007; Tanaka et al., MCN 2021), neuronal survival (Tanaka et al., Neurobiol Dis 2014), and axonal regeneration (Masuda et al., Neurobiol Dis 2022). Furthermore, GPR3 is rapidly induced in T cells by stimuli (Shiraki et al., JPS 2022). However, the potential mechanisms underlying the rapid induction of GPR3 during neuronal differentiation remain unclear. In this study, we investigated GPR3 expression during neuronal differentiation in PC12 cells. GPR3 expression was significantly up-regulated as early as 1-2 hours following serum deprivation and NGF stimulation, followed by a decline to basal levels within 6 hours of induction. A similar pattern in GPR3 expression was observed during differentiation induced by KCl, a calcium activator, or Forskolin, a cAMP activator. In contrast, the c-fos gene, a well-known immediate early gene (IEG), was induced as early as 1 hour following NGF-induced differentiation, indicating that c-fos expression occurs before GPR3 expression in response to stimuli. Furthermore, the rat GPR3 gene contains six potential cAMP response element (CRE) binding sites and one potential AP-1 binding site in its 5′ flanking region, which is relatively conserved between humans and rodents. Luciferase-based promoter assays, chromatin immunoprecipitation assays, and native elongating transcript-cap analysis of gene expression (NET-CAGE) all demonstrated that NGF-induced early GPR3 expression was mediated by the transcription factors AP-1 and CREB. Moreover, NGF-induced GPR3 expression influenced the expression of NR4A1, a target gene of the CREB transcription factor. Additionally, NGF-induced GPR3 expression modulated synapsin1 expression in an NR4A1-dependent manner. These findings suggest that GPR3 is rapidly activated in response to neuronal differentiation stimuli and may act as a type of IEG in neurons. The activity-dependent rapid induction of GPR3 may regulate CREB transcription factor-regulated genes, thereby influencing synaptic functions.

Disclosures: F. Ikawa: None. **H. Shiraki:** None. **K. Harada:** None. **I. Hide:** None. **N. Sakai:** None. **S. Tanaka:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.07/A6

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: PTEN Research Foundation
NIH R01 MH097949-01

Title: Akt is necessary for neuronal hypertrophy and excitatory synaptogenesis caused by Pten knockout

Authors: *M. L. PRINA[1], A. R. GOYETTE[2], K. TARIQ[2], A. F. ABDULKAREEM[2], L. L. DRUCKER[2], N. M. DESMET[2], M. LI[2], B. SHAFIT-ZAGARDO[3], B. W. LUIKART[1];
[1]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Mol. and Systems Biol., Geisel Sch. of Med. at Dartmouth, Hanover, NH; [3]Albert Einstein Col. of Med., Bronx, NY

Abstract: Mutations to phosphatase and tensin homolog deleted on chromosome 10 (PTEN) are a known contributor to Autism Spectrum Disorder (ASD), macrocephaly, and epilepsy. PTEN negatively regulates the mTOR signaling pathway. *Pten* knockout (KO) mouse models exhibit neuronal hypertrophy, hyperexcitability, seizures, and ASD-like behaviors. Using transgenic mouse lines and retroviral-mediated genetic alterations, we can analyze pathway outputs in response to the manipulation of various genes. In doing so, we have identified Akt as the specific downstream signaling intermediate mediating the robust neuronal hypertrophy caused by *Pten* loss. We are investigating isoform-specific roles and their contributions to this phenotype. Understanding the interactions of the downstream effectors within the mTOR pathway and how these go awry in patients with ASD, macrocephaly, and epilepsy will broaden the knowledge of these disease pathologies and identifies potential therapeutic targets.

Disclosures: M.L. Prina: None. **A.R. Goyette:** None. **K. Tariq:** None. **A.F. Abdulkareem:** None. **L.L. Drucker:** None. **N.M. Desmet:** None. **M. Li:** None. **B. Shafit-Zagardo:** None. **B.W. Luikart:** None.

Poster

PSTR433: Synapse Dynamics During Development

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Program #/Poster #: PSTR433.08/A7

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NSERC Grant #RT690332

Title: A neuro-chip approach to define electrical activity patterns of identified neurons during growth and synapse formation

Authors: *M. W. P. YACOUB[1], F. IQBAL[1], Z. KHAN[1], N. AL SHAER[1], C. JAZIEH[1], S. ALSUWAILEH[1], L. WEI[1], N. I. SYED[2];
[1]Hotchkiss Brain Inst., [2]Dept. Cell Biol. & Anat., Univ. of Calgary, Calgary, AB, Canada

Abstract: All neuronal circuits in animals rely on brain connectivity that is established during early development. This connectivity is thought to rely on precise patterns of electrical activity,

which shape both neuronal projections and synapse formation. Perturbations of precise connectivity patterns during development are thought to underlie numerous neurological disorders including epilepsy, autism, and Alzheimer's Disease, although the precise mechanisms remain unknown. This lack of fundamental knowledge in the field of neurodevelopment owes its existence to the complexity of neuronal networks in the vertebrate brain, where electrical activity cannot be continuously monitored during growth and synapse formation at the level of individual neurons. Simple model systems with individually defined neurons like Lymnaea Stagnalis (pond snails) provide the opportunity to characterize the role of electrical activity in neuronal development. LPeD1 and VD4 neurons form excitatory cholinergic synapses in the presence of conditioned media (CM), which contains trophic factors allowing us to mimic in vivo conditions in vitro. Culturing these individual neurons onto microelectrode arrays (MEAs) in the presence of CM allows for non-invasive, long-term extracellular recordings of neuronal electrical activity. Paired with simultaneous timelapse imaging, this unique animal model and MEA setup allows for the assessment of how individual action potentials (spikes) relate to morphological changes. This was done in three distinct conditions, unpaired LPeD1, paired LPeD1 and VD4, and the synaptic partners in a Soma-Soma configuration. Using a bioinformatics approach, we statistically characterized changes in activity patterns at different growth and synaptogenesis phases. We found that for paired conditions, bursting electrical activity increased in frequency, and the number of spikes belonging to a burst increased as well when approaching synapse formation. Interestingly, we observed that dendritic branching did not occur until bursting activity was present, suggesting that neuronal bursting may be a prerequisite for branching. During synapse formation we observed a unique “tetanic” activity pattern consisting of patterned transitions between tonic and bursting spikes. Analyzing the coefficient of variation in the time between spikes revealed that there is an increase in spike clustering during synapse formation. This study underscores the role of unique patterns of electrical activity throughout various developmental stages and demonstrates the importance of unique firing patterns in shaping neuronal polarity and network connectivity.

Disclosures: M.W.P. Yacoub: None. **F. Iqbal:** None. **Z. Khan:** None. **L. Wei:** None. **N.I. Syed:** None.

Poster

PSTR433: Synapse Dynamics During Development

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Program #/Poster #: PSTR433.09/A8

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: R00MH128772

Title: Genetic decoding of neural wiring in the visual system of Drosophila

Authors: *J. DONG[1], A. RATZAN[1], H. GUPTA[2], S. FAIZAL[1], R. MANN[2], E. VAROL[1]; [1]New York Univ., Brooklyn, NY; [2]Zuckerman Inst., Columbia Univ., New York, NY

Abstract: Understanding how genes influence the formation of neuronal connections has always been important for neuroscience. Recent work introduced novel approaches to identify key genes for neuronal connections in *C. elegans* (Taylor et al., 2021; Kovács et al., 2020; Qiao, 2023), while other work discussed how genes determine the selective connection of vision neurons T4 and T5 in *Drosophila* (Yoo et al., 2023). Despite these efforts, a more general model is needed to precisely decipher the relationship between genes and neuronal connections. Advancements in the electron microscope-generated connectomes give us access to the complete set of neuronal connections. The FlyWire dataset provides synaptic-level neuron morphology and connections for *Drosophila*, classifying the 37234 neurons in the right optic lobe into 227 types (Dorkenwald et al., 2023). In parallel, transcriptome datasets during different periods of visual system development allowed researchers to associate genes with specific neurons, and identified 58 neuron types from 51,000 neurons (Kurmangaliyev et al. 2020). To combine the connectome and transcriptome datasets, we focused on 39 neuron types that are shared between these two datasets. We built a connection matrix and a neuron-gene matrix based on the connectivity strength (connection probability) and gene expression level. Then we used a low-rank bilinear model to predict the connectivity strength from gene expression combination at pre/post-synaptic neurons. The model weights showed the gene pairs that contribute to the formation of synapses. We assessed the statistical significance of gene pairs using random connection matrices and 41 genes stood out from a total of 17561 genes, most of which have been reported in past research to be related to synapse formation, such as the Immunoglobulin superfamily (IgSF). Particularly, several wes accurately predicted several known gene pairs such as the Side/Beat gene connections (Side-II and Beat-VI, Side-IV and Beat-IIa, Side-IV and Beat-IIb) (Li et al., 2017). These results demonstrate that our model recovers biologically plausible gene interactions related to synaptic connectivity and paves the way for new exploratory analyses in other modal organisms and neural circuits.

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Poster

PSTR433: Synapse Dynamics During Development

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Program #/Poster #: PSTR433.10/A9

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ACCESS Scholarship, Department of Biology, Texas Womans University

Title: Deciphering the roles of rab3, 27, and 37 in neurexin trafficking: implications for synaptic function and autism spectrum disorder

Authors: *E. SWENSEN[1], S. SANSAR[2], T. GUMIENNY[1], D. L. HYNDS[3];
[1]Biol., Texas Womans Univ., Denton, TX; [2]Texas Woman's Univ., Lewisville, TX; [3]Biol., Texas Woman's Univ., Denton, TX

Abstract: Neurexins (NRXs), a family of presynaptic cell adhesion molecules, are essential for synaptic formation, differentiation, and neurotransmitter release. NRXs play a significant role in shaping the neurocircuitry underlying behavior and cognition, and their dysfunction is linked to neurodevelopmental disorders (NDDs) like autism spectrum disorder (ASD), characterized by social, communicative, and behavioral challenges. Increasing evidence suggests that altered NRX expression and function contribute to the synaptic anomalies observed in ASD. Rab GTPases, specifically Rab3, 27, and 37, are crucial regulators of vesicular trafficking and are implicated in anterograde transport. These Rabs facilitate various stages of vesicular trafficking, ensuring the delivery of cargo to their target membranes. In neurons, Rabs regulate the transport of molecules critical for synaptic strength modulation, learning, and memory. However, the specific mechanisms by which Rab3, 27, and 37 regulate NRX trafficking and synaptic integration remain unclear. Work from our lab has shown that knockdowns of Rab3, 27, and 37 inhibit NRX transport to the presynaptic membrane in the nematode, Caenorhabditis elegans. We hypothesize that Rab3, 27, and 37 are important for vesicular docking and fusion of NRX-containing vesicles. We are elucidating the explicit roles of Rab3, 27, and 37 in NRX vesicular docking and fusion at synapses and identifying their interacting partners and effectors required for NRX synaptic integration. To do this, we are employing molecular manipulations (siRNA/shRNA knockdowns or CRISPR-Cas9 knockouts), protein interaction assays (BioID, FRET), and advanced microscopy techniques (live-cell imaging, confocal, super-resolution) in established model systems (B35 rat neuroblastoma, primary rat neurons, and C. elegans. Thus far, we have determined baseline expression levels of Rab3, 27, and 37 and confirmed siRNA knockdown. We are currently analyzing which knockdowns alter anterograde NRX trafficking by tracking fluorescently-labeled NRX. Deciphering the roles of Rab3, 27, and 37 in NRX trafficking, we hope to bridge the knowledge gap between synaptic anomalies and ASD pathophysiology, paving the way for novel therapeutic strategies targeting synaptic homeostasis in NDDs.

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Poster

PSTR433: Synapse Dynamics During Development

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: National Research Foundation of Korea (RS-2023-00265581)
Innovation Research Center (RS-2023-00260454)
BK21 FOUR funded by the Ministry of Education, Republic of Korea (4120200313623)

Title: Control of spinogenesis by ER dynamics during neuronal development

Authors: *E. JANG[1], G. LEE[2], S. PARK[2];
[1]POSTECH, 77 Cheongam-Ro. Nam-Gu. Pohang., Korea, Republic of; [2]Life Sci., POSTECH, Pohang, Korea, Republic of

Abstract: Dendritic spines play a fundamental role in the information transfer between neurons and are crucial for the proper functioning of neural circuits. Various cellular processes, including regulation of calcium dynamics and lipid transport, tightly regulate dendritic spine development. The endoplasmic reticulum (ER) in dendritic spines controls the development of dendritic spines through calcium buffering and lipid transport at the contact sites between the ER and plasma membrane. Despite the functional importance of ER in the dendritic spine dynamics, the mechanism of ER dynamics in the developing spines is unknown well. Here, we demonstrate that Junctophilin3 (JPH3) is a key regulator of dendritic spine development. JPH3-positive dendritic spines regulate ER dyanmics, and its deficiency caused defective spine maturation. Retinoic acid-induced protein 14 (Rai14), an interacting partner of JPH3, was preferentially localized at JPH3-positive dendritic spines. Interestingly, Rai14 deficiency partially but effectively rescued spine maturation defects caused by JPH3 deficiency, indicating a critical role for the JPH3-Rai14 complex in ER dynamics in the dendritic spine. These results and further investigation will define the roles of JPH3 and Rai14 as crucial regulators of dendritic spine dynamics.

Disclosures: E. Jang: None. **G. Lee:** None. **S. Park:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

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Program #/Poster #: PSTR433.12/A11

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: A longitudinal analysis of the connectivity of parallel fibers to Purkinje cells in postnatal life via serial section electron microscopy

Authors: *N. DHANYASI;
Harvard Univ., Cambridge, MA

Abstract: The complex neural circuits that underlie the animal behavior are assembled during development. To uncover the developmental rules that underlie the formation and maturation of the neural circuits, we employed a connectomic approach in the mouse cerebellar cortex at five different stages during the first two weeks of postnatal life. Reconstruction of many Purkinje cells (20-50 per developmental stage), parallel fibers (300- several thousands) and the synapses between them (several thousand) at all the five stages showed significant changes taking place over postnatal development. The synaptic connectivity analysis revealed that the number of parallel fiber inputs to Purkinje cells increased more than 500 fold between birth and 14 days of age. Purkinje cells at one week of postnatal life, had generated thousands of parallel fiber-

oriented filopodia. These dendritic filopodia are innervated by parallel fibers and thus may facilitate contacts between Purkinje cell dendritic spines and parallel fibers at later ages. Concurrent with the increase in parallel fiber synapses on individual Purkinje cells, was a concomitant increase in the number of Purkinje cells each parallel fiber innervated. Additional parallel fibers were invading the more superficial parts of Purkinje cell dendrites. Together, the increase in fan-out of individual parallel fibers to innervate greater numbers of Purkinje cells and the increase in the fan-in of additional parallel fibers that innervated each Purkinje cell gave rise to a rapid increase in the total number of synapses on Purkinje cells during the second postnatal week. Importantly there was no evidence of synapse elimination: parallel fibers add connectivity as development precedes but show no signs of pruning any of these connections with Purkinje cells in stark contrast to climbing fiber synapses. The number of synapses a parallel fiber establishes per Purkinje cell is constant across the developmental stages, usually (90%) one synapse per cell. Thus, the synaptic connectivity analysis suggests an accretive model of continuous synapse addition for the formation of parallel fiber to Purkinje cell circuit. Thus, different strategies are employed by different excitatory inputs to the same postsynaptic cells.

Disclosures: N. Dhanyasi: None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.13/A12

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Synapse Formation And Pruning In The Central Nervous System Of Drosophila During Larval Development

Authors: *C. GUALTIERI, F. J. VONHOFF;
Univ. of Maryland Baltimore County, Baltimore, MD

Abstract: Synaptic pruning is a neuroplastic process influenced by neuronal activity, leading to the elimination of ectopic synapses formed during initial neuronal development. Despite its importance, the molecular mechanisms governing synaptic pruning are not fully understood. Additionally, while the disruption of synaptic pruning has been suggested as a potential cause of autism during neurodevelopment, there is limited empirical evidence supporting this hypothesis. Synaptic pruning occurs in both vertebrates and invertebrates, including Drosophila. However, most studies on synaptic pruning in fruit flies focus on the metamorphosis stage, while further studies are necessary to elucidate the mechanisms governing the pruning events known to occur earlier in development. We aimed at investigating the synaptic pruning mechanisms in the central nervous system of Drosophila during early stages of development. Notably, cIV nociceptive sensory neurons are known to form connections with Basin-4 but not Basin-1. Our hypothesis posits that in the early stages of development, cIV neurons establish connections with all Basin classes, and subsequent off-target connections are retracted through synaptic pruning.

Neuronal connections were established using the photoconvertible protein, CaMPARI, as an indicator of post-synaptic neuronal activity following presynaptic optogenetic stimulation. Revealing how the connectivity of nociceptors to basins forms in Drosophila during development, offers the basis for investigating potential failure of these processes providing insights into the molecular mechanisms regulating certain neurodevelopmental disorders.

Disclosures: C. Gualtieri: None. **F.J. Vonhoff:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.14/A13

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NINDS, NIH (R01) grant NS078375

Title: Elimination of complement proteins and CD47 rescues vulnerable synapses in spinal muscular atrophy

Authors: *D. M. FLOREZ-PAZ[1], G. Z. MENTIS[1,2];
[1]Ctr. for Motor Neuron Biol. and Dis., Depts. of Neurol., Columbia Univ., NEW YORK, NY;
[2]Pathology and Cell Biology, Columbia University, New York, NY

Abstract: The emergence of smooth overground movement in mammals requires the assembly and refinement of sensory-motor circuits in the spinal cord. We have recently reported that part of the refinement of spinal motor circuits is achieved by the action of the complement proteins C1q and C3. Importantly, CD47 also contributes to the removal of inappropriate synapses. Deviations from such mechanisms affecting synaptic refinement result in miswired circuits ultimately affecting muscle activation and body movement. However, neurodevelopmental diseases also affect synaptic function. Whether complement proteins and CD47 are involved in the synaptic elimination under neurodevelopmental neurodegenerative diseases is not well understood. To address this, we opted to investigate this fundamental question in spinal muscular atrophy (SMA), a disease that occurs during early development. The hallmarks of SMA are loss of motor neurons, muscle atrophy, and impaired spinal reflexes with dysfunction and loss of sensory synapses. Our previous study revealed that C1q, the initiating protein in the classical complement cascade play a major role in synaptic elimination of proprioceptive synapses. However, the effect of elimination of C3 and CD47 in SMA is not known. Our preliminary results using SMA mouse models crossed with CD47 ko mice revealed an improvement in righting behavior, a major phenotype in SMA mice. There was no concomitant improvement in either lifespan or body weight gain in these mice. To probe deeper into the mechanisms responsible for behavioral improvement, we investigated the function of spinal reflexes in vulnerable spinal segments using the *ex vivo* spinal cord preparation during the course of the disease. We found that the amplitude of the monosynaptic reflexes, which are mediated by

proprioceptive synapses, are significantly improved compared to SMA mice without CD47 genetic elimination. These results raised the possibility that the genetic elimination of CD47 from SMA mice could rescue vulnerable synapses that are destined to be eliminated in the course of the disease. Current efforts in the lab are focused on determining whether the elimination of CD47 has any effects on the number of proprioceptive synapses and the refinement of sensory-motor circuits. Lastly, we are exploring the effect of the genetic elimination of C3 in SMA mice, as well as the combined elimination of C3 and CD47 proteins in SMA mouse models. Our preliminary results raise the possibility that CD47 contributes to the elimination of vulnerable synapses in SMA mice and could identify it as a potential therapeutic target.

Disclosures: D.M. Florez-Paz: None. **G.Z. Mentis:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.15/A14

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: R00NS112604

Title: Developmental emergence of a Sodium Activated Potassium Channel in the prenatal human cortex and RNA therapeutic recovery of excitability

Authors: S. GOLINSKI[1], K. SORIANO[1], A. C. BRIEGEL[1], T. YU[2], ***R. SMITH**[1]; [1]Northwestern Univ., Chicago, IL; [2]Div. of Genet. and Genomics, Boston Children's Hosp., Boston, MA

Abstract: Dysfunction of sodium activated potassium channels (KCNT1, KNa1.1, also referred to as Slack channels) are associated with some of the most severe seizure related conditions in children, including a high incidence of mortality before age 3. Here, we identified the early developmental onset of KNa1.1 channels in prenatal and early neonatal human brain tissue to establish pathological origins and a therapeutic targeting timeline. Using patch clamp electrophysiology, we isolate functional KNa1.1 (KCNT1) channels in mid-gestation human neocortical neurons, that demonstrate a developmentally regulated increase in steady-state outward K+ conductances and a leftward shift in voltage dependency of activation during midgestational maturation. We also perform functional characterization of excitatory neurons derived from induced pluripotent stem cells (iPSCs) obtained from a child with a gain of function (GoF) p.R474H variant in KCNT1 associated with severe treatment-resistant epilepsy of infancy with migrating focal seizures (EIMFS). Using KCNT1-R474H patient-derived neurons, we show antisense oligonucleotide (ASO) RNA therapy knockdown of pathogenic GoF KCNT1 potassium current improves neuronal excitability and that ASO treated neurons exhibited an increased afterhyperpolarization (AHP), and normalized spiking responses and burst properties over a range of current stimulation. We also demonstrate ASO knockdown of KNa1.1 is feasible

in neurotypical mid-gestation primary human neurons. These findings suggest ASOs offer therapeutic benefit for KCNT1 patients via a shift in excitability by increasing after hyperpolarization, and that targeting functional KNa1.1 currents as early as mid-fetal gestation could offer clinical benefits prior to onset of symptoms post-birth.

Disclosures: S. Golinski: None. **K. Soriano:** None. **A.C. Briegel:** None. **T. Yu:** None. **R. Smith:** None.

Poster

PSTR433: Synapse Dynamics During Development

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR433.16/A15

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: HD083157
HD042182

Title: Synaptic connections and activity patterns in the core cranial nerve/brainstem circuit for suckling, feeding and swallowing

Authors: Z. ERWIN[1], A. HERRIGES[2], C. FLINN[3], T. M. MAYNARD[4], ***A.-S. LAMANTIA**[5]; [1]The Fralin Biomed. Res. Inst., Virginia Technol. Carilion, Roanoke, VA; [2]Neurosci., Fralin Biomed. Res. Inst. at Virginia Technol., Roanoke, VA; [3]The Fralin Biomed. Res. Inst., Virginia Technol. Carilion Sch. of Med., Roanoke, VA; [4]Fralin Biomed. Res. Inst., Virginia Technol. Carilion, Roanoke, VA; [5]Fralin Biomed. Res. Inst. Virginia Technol., Roanoke, VA

Abstract: We analyzed the identity and distribution of oropharyngeal afferents that relay mechanosensory and nociceptive information to control suckling, feeding, and swallowing (S/F/S) in wild type (WT) and *LgDel* neonatal mice with a heterozygous deletion orthologous to that in human 22q11.2 Deletion Syndrome (22q11DS). Infants with 22q11DS and neonatal *LgDel* mice have a high frequency of perinatal dysphagia: S/F/S difficulties that lead to complications including malnutrition, milk aspiration, nasal/sinus, middle ear and lung infections. We are assessing the organization and function of the brainstem circuits for S/F/S and their disruption due to 22q11 deletion. We used genetic reporters to selectively label cranial placode-derived mechanosensory or neural crest-derived nociceptive afferents from cranial ganglia that innervate facial/oropharyngeal structures essential for optimal S/F/S in early post-natal life. We analyzed synaptic puncta from these afferents in multiple brainstem sensory relay and cranial motor nuclei as well as nuclei for brainstem sensory/motor integration. Excitatory afferents have VGlut1+ synaptic endings in sensory relay nuclei: spinal trigeminal, principal trigeminal and nucleus of the solitary tract, where they interdigitate with GABAergic terminals. VGlut1+ mechanosensory terminals are also seen in several cranial motor nuclei associated with S/F/S including the trigeminal motor, facial, vagal and hypoglossal nuclei. We are currently evaluating whether this distribution of excitatory/inhibitory afferents changes in neonatal *LgDel*

mice. In parallel, we used cFOS to map activation of brainstem nuclei in response to re-initiating S/F/S after 2 hours of fasting. Neuronal activity is enhanced selectively by return to nursing vs. fasted control mice. The foci of enhanced activity based upon cFOS labeling include core sensory relay and motor nuclei likely essential for S/F/S plus a limited number of interneuron/integrative nuclei including the parabrachial nucleus. We are currently comparing WT vs. LgDel numbers of cFOS+ cells in response nursing versus fasting. Together our results define a "core" cranial nerve/brainstem circuit for sensory/motor integration necessary for optimal S/F/S.

Disclosures: Z. Erwin: None. **A. Herriges:** None. **C. Flinn:** None. **T.M. Maynard:** None. **A. LaMantia:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.01/A16

Topic: A.07. Developmental Disorders

Support: NSCT 110-2926-I-A49-001-MY4
NSCT 111-2823-8-A49-003
NSCT 112-2823-8-A49-001
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Mt. Jade Young Scholarship Award, Ministry of Education, Taiwan
Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan
Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

Title: Exploring Autism Developmental Patterns through Brain Age Prediction Model Based on Structural Brain Magnetic Resonance Imaging Features: An Autism Brain Imaging Data Exchange Dataset Research

Authors: *I.-J. CHI[1], A.-C. YANG[2];
[1]Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]Inst. of Brain Sci., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Introduction: Brain age gap is often regarded as a significant marker with implications for development. Autism is a dynamic developmental condition, suggesting it may exhibit distinct developmental patterns and interpretations of brain age gaps compared to typically developing individuals. Therefore, our objectives were (1) To construct developmental patterns of brain age gaps based on 4 brain structural features. (2) To investigate the implications

of variations in brain age gaps within the autistic group. **Methods**: We employed preprocessed structural MRI from 345 autistic and 412 typically developing (TD) individuals aged 6-48 years, sourced from the Autism Brain Imaging Data Exchange dataset. Brain features— gray matter volume, subcortical volume, surface area, and cortical thickness—were extracted for each participant. The TD group was split into training (n = 247) and testing (n = 165) datasets, balanced for sex and age. Utilizing Gaussian process regression, we trained the brain age prediction model on the TD training dataset with five-fold cross-validation and evaluated it using the TD testing dataset, recording the corrected brain age gaps of children in the TD testing dataset and autism group. Four developmental patterns were constructed based on the mean of brain age gap in each age group, using partially overlapping sliding age-windows. Within the autism group, individuals were divided into those with positive or negative brain age gaps, and t-tests were employed to investigate demographic and behavioral differences. **Results**: Fair model performance was observed among the training, testing, and autism groups of 4 models (Mean Absolute Errors: 3.57-6.59, 3.51-6.16, 3.39-6.24). Distinct developmental trends in brain age gap patterns are evident across 4 features. In whole-brain gray matter volume and cortical thickness, autistic individuals with positive brain age gap exhibited greater receptive skills (12.0±2.63) than those with negative brain age gap (10.6±3.08, $p < .05$). In subcortical volume, autistic individuals with positive brain age gap showed more autistic traits (12.3±3.94) and lower expressive scores (9.9±1.97) than those with negative brain age gap (autistic traits: 11.1±3.69, expressive scores: 11.3±2.58, $p < .05$). Those results all confirmed by permutation tests. **Conclusions**: The brain age gap patterns reveal distinctive developmental patterns in autism, offering a profound exploration of autism's development from varied structural viewpoints. Our results showcase varied representations of brain age gaps across different feature models, highlighting the importance of interpreting these gaps uniquely in autism.

Disclosures: I. Chi: None. **A. Yang:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.02/A17

Topic: A.07. Developmental Disorders

Title: Neural mechanisms of nucleus accumbens deep brain stimulation for self-injurious behaviours in Autism Spectrum Disorder

Authors: *K. ZHANG[1,3], R. MATIN[4,3], M. EBDEN[4], C. GORODETSKY[5], K. MITHANI[4,6], J. ELLEGOOD[2], J. P. LERCH[2], F. GOUVEIA[4], G. M. IBRAHIM[6,3,4];
[1]Neurosciences and Mental Hlth., [2]Mouse Imaging Ctr., The Hosp. For Sick Children, Toronto, ON, Canada; [3]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [4]Neurosciences and Mental Hlth., [5]Div. of Neurol., [6]Div. of Neurosurg., The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Children with Autism Spectrum Disorder (ASD) often manifest self-injurious behaviours (SIB) that may become severe and refractory with limited treatment options. These SIBs may lead to disability or death and deprive children and their families of quality of life. Deep brain stimulation (DBS) at a locus of neural circuitry implicated in SIB, the nucleus accumbens (NAcc), has recently been developed in a world-first phase I clinical trial at the Hospital for Sick Children as a potential treatment for affected children (ClinicalTrials.gov identifier: NCT03982888). However, the neural underpinnings of NAcc stimulation for SIBs are poorly understood, and multi-disciplinary translational studies using both pre-clinical animal models and clinical data are necessary to explore the mechanisms of disease and treatment. Here, we evaluated the behavioural and neuroanatomical changes induced by NAcc-DBS in the BTBR *T*$^{+}$ *Itpr3*^{tf}/J (BTBR) mouse model of SIB and ASD to provide insights into the pathophysiology underlying the treatment being offered in the phase I clinical trial at the Hospital for Sick Children. BTBR mice received chronic DBS or sham stimulation to the bilateral NAcc, followed by a series of behavioural tests evaluating ASD-related phenotypes (self-injurious, repetitive, anxiety-like, and social behaviours). Neurocircuitry influenced by NAcc-DBS was assessed using high-resolution magnetic resonance imaging, deformation-based morphometry, and MAGeTbrain (Multiple Automatically Generated Templates Brain Segmentation Algorithm) pipelines. We found that chronic, high-frequency NAcc-DBS reduced repetitive and SIBs, and improved sociability among BTBR mice. These behavioural improvements were associated with reduced volume in several brain areas thought to be critical for SIB regulation, such as the somatomotor and somatosensory cortices, anterior cingulate cortex, caudate putamen, hypothalamus, and periaqueductal grey. These findings will provide mechanistic insight to the world-first pilot trial of NAcc-DBS in children with severe SIB and ASD. Results from this study will advance our understanding of the neural circuitry subserving SIB, potential plasticity changes induced by stimulation of the NAcc, and provide foundational evidence to establish NAcc-DBS as a therapy for affected children.

Disclosures: K. Zhang: None. **R. Matin:** None. **M. Ebden:** None. **C. Gorodetsky:** None. **K. Mithani:** None. **J. Ellegood:** None. **J.P. Lerch:** None. **F. Gouveia:** None. **G.M. Ibrahim:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.03/A18

Topic: A.07. Developmental Disorders

Support: NIH grant HD084289

Title: Ondansetron treatment attenuates the effects on prenatal stress on repetitive motor behaviors in adolescent male Fmr1 knockout mice

Authors: *M. E. RAGOZZINO[1], J. P. SEVIGNY[2], K. AMODEO[3], H. DZIELAWA[1]; [1]Psychology, Univ. of Illinois Chicago, Chicago, IL; [2]Grad. Program in Neurosci., Univ. of Illinois, Chicago, Chicago, IL; [3]Univ. of Illinois Chicago, Chicago, IL

Abstract: Fragile X Syndrome (FXS) is an intellectual disability syndrome, in which one-third of affected individuals exhibit autistic features. FXS is caused by transcriptional silencing of *FMR1*, a gene encoding an RNA-binding protein. FXS individuals with autism spectrum disorder (ASD) exhibit heterogeneity in symptoms. There is increasing support that ASD arises from a complex interaction of environmental and genetic risk factors, including for monogenic syndromes, i.e. FXS. Past studies indicate that maternal stress during pregnancy may increase risk for ASD by glial reactivity producing neuroinflammatory responses in offspring. Past findings suggest that 5-HT_3 receptor antagonist treatment reduces glial reactivity and elevated central cytokine release. Thus, treatment with a 5-HT_3 receptor antagonist treatment may be effective in attenuating the effects of prenatal stress on ASD risk. The present experiment investigated whether the 5-HT_3 receptor antagonist, ondansetron attenuated the effects of prenatal stress on repetitive motor behaviors in male Fmr1 knockout (KO) and wildtype mice. Pregnant dams were exposed to two 30 minute restraint stress sessions during gestation days 10-16. At 4 weeks of age, offspring received a daily injection of ondansetron (1 mg/kg) or saline for seven consecutive days. One day after the last injection, mice received a nesting removal test (repetitive digging behavior) and zero maze test (anxiety-like behavior). Prenatal stress elevated digging behavior in WT and Fmr1 KO mice with a significantly greater effect in Fmr1 KO mice. Preliminary findings indicate that subchronic treatment with ondansetron significantly attenuated the prenatal stress induced elevation in repetitive digging behavior in both WT and Fmr1 KO mice. Prenatal stress had no effect on locomotor activity in the nesting removal test or anxiety-like behavior in the zero maze, nor did ondansetron treatment affect these measures. These results suggest that prenatal stress may interact with genetic factors to increase risk for autism-like behaviors. Further, the effects of prenatal stress on autism-like behaviors is attenuated by a 5-HT_3 receptor antagonist possibly by producing an anti-inflammatory response in neural circuity underlying repetitive behaviors.

Disclosures: M.E. Ragozzino: None. **J.P. Sevigny:** None. **K. Amodeo:** None. **H. Dzielawa:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.04/A19

Topic: A.07. Developmental Disorders

Support: NIMH KO1MH119540
P50 HD103556

Title: Neonatal gonadal hormone dysregulation induces social and fear deficits

Authors: *E. M. HAGAN[1], P. QUINONES[2], D. PREUSCHL[3], C. TESAR[3], S. L. FERRI[3]; [1]Univ. of Iowa, Iowa City, IA; [2]Neurosci. & Pharmacol., Univ. of Iowa, Iowa City, IA; [3]Stead Family Dept. of Pediatrics, Univ. of Iowa, Iowa City, IA

Abstract: Social behavior is a critical function which dictates many facets of well-being, including mental and physical health, and overall quality of life. Disruption to these social processes are exhibited in neuropsychiatric and neurodevelopmental disorders such as schizophrenia and autism spectrum disorder (ASD). Research has found that there is a male sex bias in neurodevelopmental disorders, such as in ASD where males are four times are likely to be diagnosed with autism as females. The mechanism of this robust sex bias is not well understood. Here, we used neonatal injections of gonadal hormones as a novel experimental system to disrupt sex-specific developmental pathways in mice to determine their effects on behaviors relevant to ASD. We found that testosterone administration on the day of birth, which is equivalent to mid gestation in humans, induces male-specific deficits in social approach and fear memory. These deficits were only present when the injection was given on the day of birth and not at postnatal day 18. Furthermore, while testosterone injected on the day of birth did cause social and contextual fear conditioning deficits, it did not affect anxiety-like behavior on an elevated zero maze or body weight over development. Administration of D-cycloserine, a NMDAR partial agonist, which has been shown to ameliorate social deficits preclinically, alleviated the testosterone-induced social and fear deficits. Surprisingly, estradiol given on the day of birth did not lead to female or male specific social deficits which suggests that aromatization of testosterone to estradiol is not the cause of the testosterone induced social deficits in males. Brain wide activity mapping has shown altered brain activation in areas of the brain associated with social behaviors such as the medial prefrontal cortex and basolateral amygdala. Currently we are investigating the mechanisms of these sex specific vulnerabilities to social and fear deficits. These findings will aid in advancing the current understanding of how the brain is susceptible to social impairments and help identify novel treatment targets.

Disclosures: E.M. Hagan: None. **P. Quinones:** None. **D. Preuschl:** None. **C. Tesar:** None. **S.L. Ferri:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

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Program #/Poster #: PSTR434.05/A20

Topic: A.07. Developmental Disorders

Support: Conahcyt Mexico Scholarship 813946 to NLQ
Conahcyt Mexico Posdoc 391161 to AGG
Conahcyt Mexico Scholarship 761616 to SZE

Title: Autism in home: negative feedback between children and families in Xalapa, Mexico.

Authors: N. LAUREAN QUIROGA[1], A. G. GUTIERREZ[2], S. ZEPEDA ESQUIVEL[3], M. HERNANDEZ[4], R. TOLEDO-CARDENAS[3], D. HERRERA-COVARRUBIAS[3], G. A. CORIA-AVILA[5], *J. MANZO[3];
[1]Univ. Veracruzana, Xalapa, Veracruz, Mexico; [2]Biomed. Sci., [4]Inst. de Investigaciones Cerebrales, [3]Univ. Veracruzana, Xalapa, Mexico; [5]Inst. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Ver, Mexico

Abstract: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by difficulties in social communication, alongside patterns of restricted interests and repetitive behavior. Furthermore, the challenges faced by children with ASD within their social environments significantly influence their quality of life. Among these environments, the family context plays a crucial role, presenting additional challenges for the well-being of the affected child. Thus, it becomes imperative to analyze how the presence of autism impacts family dynamics and, conversely, how these modifications influence the environment of ASD children and impact their development. To elaborate this analysis, we examined various aspects of family life in which children are raised. Our study focused on 63 children diagnosed with ASD and 57 neurotypical children, aged 4 to 16, and their families residing in Xalapa, Veracruz State, Mexico. Using standardized assessments such as the Wechsler Intelligence Scale and the Autism Diagnostic Interview-Revised, we compared results between the two groups. Our findings revealed that most children with ASD exhibited a total intelligence quotient (TIC) below average, while most neurotypical children scored within the average or above-average range. Families of ASD children with average or below-average TIC faced high rates of divorce or abandonment by a parent, particularly when the ASD severity was categorized as level 2. Despite these challenges, most ASD children attended school, with approximately 40% experiencing bullying. In the face of such circumstances, families of ASD children expressed two primary concerns: difficulties in language and communication, and emotional crises. In contrast, neurotypical children did not exhibit significant issues in these areas. These results shed light on the social impact of autism within the home environment, which, in turn, affects the developmental pathway of ASD children. In addition to addressing the unique challenges associated with autism, we advocate for a multi-level approach to confronting autism, addressing both individual needs and family structures. By providing comprehensive support at these levels, we can better enhance the well-being and development of children with ASD, ultimately fostering more inclusive and supportive environments for individuals and families affected by this condition.

Disclosures: N. Laurean Quiroga: None. **A.G. Gutierrez:** None. **S. Zepeda Esquivel:** None. **M. Hernandez:** None. **R. Toledo-Cardenas:** None. **D. Herrera-Covarrubias:** None. **G.A. Coria-Avila:** None. **J. Manzo:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.06/A21

Topic: A.07. Developmental Disorders

Support: Shota Rustaveli National Science Foundation Grant F

Title: Rodent Propionic Acid Model of Autism. Social Behavior, Anxiety-like Behavior and Ultrastructure of Amygdala

Authors: *M. G. ZHVANIA;
Ilia State Univ., Tbilisi, Georgia

Abstract: Autism spectrum disorder (ASD) is characterized by stereotypic activities, limited interests, communication disorder, cognitive and emotional deficiencies. ASD's neurobiological basis comprises structural deviations in many brain regions. Basolateral amygdala, the component of the social brain, plays a central role in social communications, attachment behavior and emotional memory. Given that the study of amygdala in autistic brain is important importance. Propionic acid (PPA), short-chain fatty acids made by enteric bacteria, has many positive functions; however Increased level of PPA is associated with various neurological disorders, including autism. Chronic injection of PPA in rodents affects social skills, cognition and produces other alterations, compatible to whose, observed in individuals with ASD. However, little is known regarding structural effects of PPA on the brain. Here we describe the effect of acute administration of low dose of PPA (175 mg/kg) on social behavior, anxiety-like behavior, and the ultrastructure of basolateral amygdala in adolescent male (P30-35) Wistar rats. Behavioral and electron-microscopic studies were performed 10 days after treatment. PPA-treated rats show decreased interest for social stimulus and unchanged interest to unsocial stimulus. Behavioral data also show that the regime of treatment has no effect on anxiety-related behavior. In 11% of neurons, at an electron microscopic level focal or diffuse chromatolysis, swollen or destructed cytoplasmic organelles, increased osmiophily of cytoplasm, destructed dendrotubules, large presynaptic terminals with a few synaptic vesicles, swollen astrocytes and activated microglia were seen. Total area of axodendritic presynaptic terminals, the area of presynaptic mitochondria and the number of porosomes were significantly increased. In general, the data indicate that in rodents even low doses of PPA affects social behavior and amygdala's ultrastructure. Ultrastructural data should indicate moderate alterations in neurotransmission and functional networks of amygdala.

Disclosures: M.G. Zhvania: None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.07/A22

Topic: A.07. Developmental Disorders

Title: Correlation of inflammatory cytokines, synaptic proteins and growth factors with developmental outcomes in autism spectrum disorder: A cross sectional study.

Authors: *A. JAIN;
King George Med. Univ. in collaboration with Univ. of Rajasthan, India, Lucknow and Jaipur, India

Abstract: Correlation of inflammatory cytokines, synaptic proteins and growth factors with developmental outcomes in autism spectrum disorder: A cross sectional study. Ayushi Jain*[1,2], AA Mahdi[2], VK Mehta[3], M Sharma[1]., PJ John[1], AA Saifee[3].
1.Department cognitive neuroscience & Zoology, University of Rajasthan, Jaipur, India, 2. Department Biochemistry, King George Medical University, Lucknow, India, 3. Department Neurology, Geetanjali Medical University, Udaipur, IndiaPurpose: Neurodevelopmental disorders are complex, multifactorial and underscored by heterogeneous symptomology. Oxidative stress, inflammatory cytokines and sleep play a pivotal role in the pathogenesis of developmental disorders. Our study explored the underlying role of interleukin-1β (IL-1β), IL-6, nerve growth factors (NGF), free radicals in autism spectrum disorder (ASD) with respect to the cognitive and sleep. Methods: Ninety-five suspected ASD children (5-12 years) were compared to controls (n=90). Diagnosis by medical specialists, based on the International Classification - ICD-10, DSM-5 and CARS score. Serum IL's (1L-1β, IL-6), synaptic protein (α-synuclein), growth factor (NGF) were measured by ELISA. Saliva parameters for free radicals were analyzed by standardized methods. Children's Sleep Habits Questionnaire (CSHQ) scores were used to evaluate sleep. Results: Mean salivary values of peroxidase and superoxide dismutase activity increased significantly ($P < 0.05$) as compared to the controls. The lower plasma nerve growth factor and α-synuclein level in ASD group was highly significant as compared to controls. The mean concentrations of IL-1β, Il-6 and CRP in the ASD group showed a significant rise ($P < 0.05$) as compared with the control group. Results inferred that there were positive correlations between the markers, behavior recurrence and hyperactivity, but they did not correlate with family history and sleep. ASD group was found to have greater sleep disturbance as compared to the controls, total CSHQ score ($p < 0.005$)Conclusions: This study demonstrates the profound impact of oxidative metabolism, inflammatory cytokines and growth factors on ASD, sleep and cognition. The result supports the possibility of using an appropriate selection of serum cytokine for early ASD diagnosis and emphasizes the need to standardize quantitative methods for serum analysis. Furthermore, the findings contribute to the ongoing efforts toward identification of early biological markers specific to sub phenotype of ASD & rehabilitation.

Disclosures: A. Jain: None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.08/A23

Topic: A.07. Developmental Disorders

Support: NINDS Grant R01NS091220

Title: Early life behavior in Arid1b haploinsufficient mice becomes more ASD-like with age

Authors: *T. L. FORD[1], A. SMITH[2], W.-Y. KIM[1];
[1]Biol. Sci., Kent State Univ., Kent, OH; [2]Biol. Sci., Kent State Univ., Rochester, NY

Abstract: Title: Early life behavior in *Arid1b* haploinsufficient mice becomes more ASD-like with age.Throughout research into autism spectrum disorder (ASD) in rodent models, data is often presented in adult models. However, recent research into ASD mouse models shows differences in autism-like behavior in early life compared to adulthood. AT-Rich Interactive Domain 1B (ARID1B) is a chromatin modifying protein and is involved in early cell development. Although *ARID1B* haploinsufficiency is known to cause ASD, very little is known about what this means in early life. Using *Arid1b* heterozygous (haploinsufficient) mice as a model of ASD, we have replicated behavioral tests at younger ages that have shown significant differences in adulthood. We targeted specific ages that act as important developmental markers: PN30 (post weaning adolescence), PN60 (sexual maturity), and PN120 (adulthood where most published results are from). Results showed that *Arid1b* haploinsufficient mice had behavior more wild type-like at PN30 during all three tests performed (open field test, novel object test, and 3-chamber sociability tests). As they aged, *Arid1b* heterozygous mouse behavior began to diverge further from their wild type counterparts. These results reached significant differences at PN120. These mice also had mRNA collected immediately after the 3-chamber test to determine if brain regions related to social behavior express different levels of oxytocin at different ages. Oxytocin expression was significantly decreased in the paraventricular nucleus (PVN) at PN120 while it was not the case during early life at PN30. Oxytocin levels were also different in other regions such as the ventral tegmental area (VTA), bed nucleus of stria terminalis (BNST), and the amygdala during the progress of development. Together, our data reveals that *Arid1b* haploinsufficiency may lead to ASD-like behavior diverging from typical behavior as mice age.

Disclosures: T.L. Ford: None. **A. Smith:** None. **W. Kim:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.09/A24

Topic: A.07. Developmental Disorders

Support: DoD CDMRP Autism Research Program (ARP) Award HT9425-23-1-0395

Title: Characterizing isolation induced vocalizations in a rat model of autism

Authors: *A. M. VAIDYA[1], D. GAUTHIER[2], B. D. AUERBACH[3];
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Abstract: Fragile X syndrome (FXS) is a common neurodevelopmental disorder and the leading monogenetic cause of autism. FXS is caused by the transcriptional silencing of the FMR1 gene and loss of FMRP, a protein crucial for brain development. Like the greater autistic population, a majority of FXS individuals present with altered social communication and delayed speech and language development. Rats exhibit a form of vocal communication by emitting ultrasonic vocalizations (USVs) in response to a wide range of stimuli and social conditions. Importantly, USV call structure is indicative of behavioral state and distinct call types are emitted under different social conditions, suggesting that USVs are a model for social communication in rodents. In order to model communicative impairments in FXS, we examined isolation-induced USVs across development in a Fmr1 KO model of FXS. USVs were recorded from littermate Fmr1 KO and wild-type littermate rat pups briefly isolated from their mothers at various points along early post-natal development(p3, p6, p8, p10, p14, p18 and p21). We observed dynamic changes to USV call-rate and structure across development, with call number and complexity increasing from birth to ear opening (p14). While there was no genotype difference in call rate across developmental time-points, Fmr1 KO rats exhibited significant delays in syntax development, resulting in less complex call structure. These results suggest that USV characterization in Fmr1 KO rats may provide a useful model for understanding social communication deficits in FXS, with the potential to provide insight into the underlying mechanisms and aid in the development of tools for early diagnosis and intervention.

Disclosures: A.M. Vaidya: None. **D. Gauthier:** None. **B.D. Auerbach:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.10/A25

Topic: A.07. Developmental Disorders

Title: Evaluating the Therapeutic Potential of GM-CSF to Target Behavioral Phenotypes and Brain Pathology in Mouse Models ofAutism Spectrum Disorder

Authors: *M. A. HAQ, C. HEITMANN, A. C. WANG, H. J. CHIAL, H. POTTER, M. AHMED;
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits, repetitive/restricted behaviors, and cognitive impairments, affecting 1 in 16 children in the U.S. and 1 in 100 children globally, with males being diagnosed 3-4 times more frequently than females. Although some ASD-associated clinical and behavioral phenotypes are well-studied, their relationship with brain pathology remains poorly understood. Granulocyte-macrophage colony-stimulating factor (GM-CSF), an FDA approved immune system modulator used for other conditions, has shown promise in improving brain pathology

and cognition in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Down syndrome (DS) in animal models and in clinical trials for AD and PD. Our recent findings demonstrate that GM-CSF treatment rescues cognitive impairments, reduces astrogliosis, increases the numbers of interneurons in the hippocampi, and reverses a prominent deficit in the number of Purkinje cells in the cerebellum of the Dp16 mouse model of DS. Many of these phenotypes are similar to abnormalities seen in human ASD and in animal models of ASD. The cerebellum is a major focus in ASD research due to its association with many of the social, repetitive, and behavioral phenotypes in ASD. Here, we are testing whether five weeks of GM-CSF treatment (5 μg/day, 5 days/week) rescues social, repetitive, and cognitive behavioral phenotypes and improves underlying brain pathology (i.e., numbers and morphologies of Purkinje cells in the cerebellum and of interneurons in the cortex and hippocampus) in the BTBR *T+ Itpr3tf/J* (BTBR) and Fmr1 knockout (KO) mouse models of ASD. Our preliminary studies reveal a trend towards reduced Purkinje cell numbers in the cerebellum of BTBR and Fmr1 KO mice. We have also found that GM-CSF treatment rescues deficits in learning flexibility as measured in the radial arm water maze (RAWM) in 3-month-old male Fmr1 KO mice. Future experiments will examine additional ASD-related brain pathologies, assess learning flexibility in female Fmr1 KO mice and in both sexes of BTBR mice, and use other behavioral assessments to test whether GM-CSF treatment reverses or improves social, repetitive, and cognitive behavioral phenotypes in both sexes of the BTBR and Fmr1 KO models of ASD. These outcomes will help determine the potential of GM-CSF to restore social and cognitive deficits in two different mouse models of ASD, the results of which will help to propel future clinical trials.

Disclosures: M.A. Haq: None. **C. Heitmann:** None. **A.C. Wang:** None. **H.J. Chial:** None. **H. Potter:** None. **M. Ahmed:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.11/A26

Topic: A.07. Developmental Disorders

Title: Valproic acid-induced autistic-like behaviour and altered ultrasonic vocalizations in mice are sex dependent and can be potentially rescued by S-adenosyl-methionine

Authors: *D. GOROBETS[1,2], M. BECKER[3], A. JUROVIESKY[3], B. E. ECHEFU[3], A. ORNOY[4,2];
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Abstract: Valproic acid (VPA), a potent antiepileptic drug and mood stabilizer, is an epigenetic modulator used in mice to induce autism spectrum disorder (ASD)-like behaviour. S-adenosyl-methionine (SAMe) having antagonistic epigenetic effects to VPA action (Weinstein-Fudim et.

al, 2020) can potentially ameliorate autistic phenotype in mice elicited by VPA. We treated pregnant mice on gestational day (GD) 12 by VPA in concentrations of 300 and 600 mg/kg, to induce autistic like behaviour in offspring. Separate mice were administered VPA in combination with daily SAMe (30 mg/kg) during GD 12-14 to prevent potential VPA impact, or with SAMe alone. For behavioral phenotyping of autistic-like patterns in offspring, during adulthood (days 55-60) we utilized open field (OF) test to evaluate mice extent of anxiety and three-chamber test (3CHT) to assess sociability. Working memory was assessed using spontaneous alternation Y-maze test. Additionally, during early postnatal period - postnatal days (PND) 3.8 and 14 we assessed emission of the ultrasonic vocalizations (USVs) in mice offspring. We found that at PND3, VPA induced an increase of USVs emission in male offspring, and a decrease in females, only at higher VPA dosage. At PND8 and 14 we observed a lower vocalizations emission only in females. SAMe co-treatment rescued alternations of USVs emission in females only at PND3 at 600mg/kg and at PND14 at 300 mg/kg. In males, the effect of VPA on USVs emission was potentiated by SAMe at both PND 8 and 14. Behavioural phenotyping revealed reduced socialization in 3CHT in VPA-treated females, but not males, SAMe co-administration lead to partial rescue of the VPA effects. SAMe itself did not have any impact on the sociability of the adult offspring. Y-maze test revealed a decay of working memory in all male offspring, but not in females. OF test demonstrated that prenatal treatment by VPA has an anxiogenic effect in adult male offspring and anxiolytic in female. SAMe co-treatment led to an increase of anxiety in both sexes. SAMe treatment itself had no impact in OF test in both sexes. Our findings provide evidence that prenatal VPA treatment induces autistic-like phenotype resembling changes observed in human (Weinstein-Fudim, et. al, 2019). SAMe, co-administrated to VPA can partially ameliorate phenotypical changes done by the latter. In addition, we demonstrated sex related differences in the behavioral presentations of many of the ASD -like features induced by VPA. Our results may open a perspective for SAMe, as a principal physiological methyl donor and approved food additive, to become a potential pre-treatment or supplement allowing to reduce the risk of children with ASD.

Disclosures: D. Gorobets: None. **M. Becker:** None. **A. Juroviesky:** None. **B.E. Echefu:** None. **A. Ornoy:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

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Program #/Poster #: PSTR434.12/A27

Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI Grant 20H00600
Joint Usage/Research Program of Medical Institute of Developmental Disabilities Research, Showa University

Title: Gaze attraction toward higher-order visual features in autism spectrum disorder

Authors: *S. YOON[1], N. ASAMI[1,3], M. EGUCHI[1], K. AKAMATSU[1], H. OTA[4], M. NAKAMURA[4], T. OKIMURA[4], R.-I. HASHIMOTO[4,5], T. ITAHASHI[4], R. AOKI[4,5], Y. MIYAWAKI[1,2];
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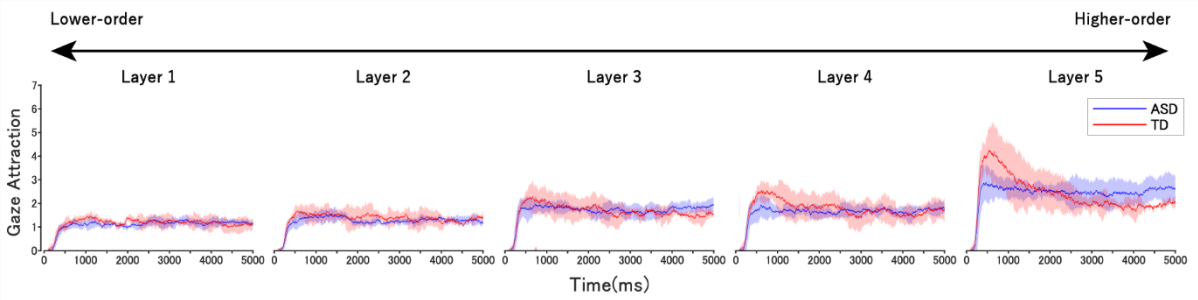
Abstract: Atypical attention toward visual stimuli of autism spectrum disorder (ASD) is known as a source of difficulties in their social life, and its neural mechanisms are expected to be revealed. A previous study (Wang et al., 2015) showed that the gaze of ASD individuals is different from typically developing (TD) in coarse levels of visual features and less attracted to locations including faces and social components, but it remains unclear how the differences can be changed according to the complexity of visual features. To address this issue, we used deep convolutional neural network (DCNN) to extract visual features with different complexity along the DCNN's hierarchy and evaluated the gaze attraction to each visual feature quantitatively. ASD and TD individuals participated in experiments after granting written informed consent. Eye movements were monitored while participants viewed a series of naturalistic scene images. Hierarchical visual feature maps for each presented image were generated by back-projecting the activation in each layer of DCNN. We then examined how the gaze was attracted to these visual features in both space and time. Results showed that ASD group had stronger bias towards higher-order visual features than lower-order visual features, similar to TD group (Fig. 1), but the difference between two groups was found in the time course. TD group exhibited a marked transient peak in the gaze attraction followed by gradual decline over time, particularly for the higher-order visual features. In contrast, ASD group lacked a discernible peak for any levels of visual features. These results indicate that the gaze characteristics of ASD individuals vary over the level of visual-feature complexity, showing the most intense attraction toward higher-order visual features, but its dynamics are different from TD individuals. Together with the previous study, these findings suggest that atypicality of gaze and underlying attention in ASD individuals might manifest in response to different complexity in visual features, in particular, strongly present in its temporal dynamics.



Disclosures: S. Yoon: None. **N. Asami:** None. **M. Eguchi:** None. **K. Akamatsu:** None. **H. Ota:** None. **M. Nakamura:** None. **T. Okimura:** None. **R. Hashimoto:** None. **T. Itahashi:** None. **R. Aoki:** None. **Y. Miyawaki:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.13/A28

Topic: A.07. Developmental Disorders

Support: FC2022-2024 PD
CONACYT/PEI 2011/3 ProInova/157118

Title: Social cognition and locomotor activity in the C58/J strain, a possible murine model of Autism Spectrum Disorder

Authors: K. OCAMPO ORTÍZ[1], E. G. IBARRA CORONADO[2], M. FUENTES-CANO[1], D. J. BUSTAMANTE VALDEZ[1], ***P. DURAN**[1];
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Abstract: Autism spectrum disorder (ASD) is a multifactorial neurodevelopmental disorder. Several of the behaviors and alterations that individuals with ASD share, within a spectrum, may be linked to a deficit in their circadian rhythm regulation, for example, the deficit in social cognition that has been related to deficiencies in interaction, such as the inability to initiate/develop personal interactions, lack of empathy, deficit in speech development, etc. Animal models have made it possible to find links between alterations of the circadian oscillator and disorders, allowing the understanding of both physiology and different social behaviors. The C58/J mouse strain spontaneously presents autistic-like behavior from the neonatal period to adulthood, including deficits in sociability, altered communication, and motor stereotypy. The main objective was to analyze the rhythm of locomotor activity and the capacity for social interaction in the C58/J strain. 20 C57BL/6 mice, as the control strain, and 18 C58/J as an experimental strain were subjected to a locomotor activity recording (LO 12:12 ZT0=7am) and a behavioral test: a three-chamber paradigm to evaluate social behavior (social affiliation/motivation). The results highlight the presence of alterations in the circadian synchronization of the activity/rest rhythm in the C58/J mouse, such as a decrease in the activity period, a delay in the active (α) phase, and an advance in the sleep or rest (ρ) phase. On the other hand, in the behavioral test, the C58/J strain showed an increased preference for the central area and no preference for the chamber where the familiar or strange subjects were placed, both at 3 and 10-minute tests. Our results suggest a modification in the control of the biological clock of the C58/J strain, which would explain some of the alterations in both the sleep-wake cycle and, consequently, behavioral ones (deficits in social interaction and increased stereotypies and repetitive behaviors), which have been reported both in this model and in humans with ASD and are part of the most evident in the disorder. When reproduced in this strain, these parameters help us to validate C58/J as a possible model to study ASD in addition to lower-order repetitive behaviors (motor stereotypies) already reported.

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Poster

PSTR434: Neurodevelopmental Disorders and Behavior

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Program #/Poster #: PSTR434.14/A29

Topic: A.07. Developmental Disorders

Support: NIH R01 NS045193
NIH R01 MH115750
NSF PHY-1734030

Title: Machine vision-based analysis of dyadic interactions in wildtype and autism model mice

Authors: *R. TAM[1], M. KISLIN[2], J. SHAEVITZ[3], S. S.-H. WANG[2];
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Abstract: Individuals with autism spectrum disorder (ASD) have difficulty interpreting social cues and understanding the mental states of others; conversely, neurotypical individuals may also experience difficulty interpreting the behavior of individuals on the spectrum. To study social recognition and interaction in mouse models of autism, we used machine vision to automatically categorize moment-to-moment behavioral interactions between wild-type mice and L7-Tsc1 mice, a cerebellum-specific transgenic mouse model which displays impaired social interactions and a lack of social preference. After recording mice in a large (45 cm) and small (30 cm) open-field square arena, we used SLEAP for multi-animal pose tracking. Wild-type and L7-Tsc1 mutant mice were assigned a partner mouse of either strain. We analyzed posture dynamics from over 7.5 million frames (80 Hz) with an unsupervised computational approach (MotionMapper) and quantified seven distinct behavioral clusters in a mouse-centric space. We used centroid metrics and behavioral clusters to identify context-dependent effects. The presence of a freely moving social partner and a smaller arena size enhanced closer interactions between mice and significantly altered behavioral occupancies. A smaller arena size also led to higher behavioral synchrony between wild-type mice than in wild-type/L7-Tsc1 mixed pairs. In the large arena, we used Jensen-Shannon divergence to quantify the similarity of a mouse's behavior to itself at different distances to its partner and found three zones of distinctive interaction patterns. The nearest-distance pattern was disrupted when a L7-Tsc1 mouse was present or in the smaller arena. At the start of bouts of interaction, wild-type mice approached L7-Tsc1 mice more slowly than they approached other wild-type mice. In summary, ASD-related genetic alteration affects both near-distance interactions and the approach behavior towards them by wild-type mice. We are now analyzing the dynamics and internal states of wild-type and L7-Tsc1 mice as they encounter one another for the first time.

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Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.15/A30

Topic: A.07. Developmental Disorders

Title: Relationship Between Level of Light Pollution at Night and Rates of Sleeping Disorders in Patients with Autism Spectrum Disorder

Authors: *D. S. BHANDAL[1,2], J. B. TUSCHHOFF[1,2], D. M. DAVIES[1], K. NGUYEN-NGO[2], C. S. COLWELL[4], C. A. GHIANI[3];
[1]Sch. of Med., Univ. of Missouri, Kansas City, Kansas City, MO; [3]Pathology, [2]UCLA, Los Angeles, CA; [4]Psychiatry and Biobehavioral Sci., Univ. of California - Los Angeles, Los Angeles, CA

Abstract: Autism spectrum disorder (ASD) is often associated with disturbances in circadian rhythms which manifest with difficulties in falling and staying asleep. Sleep disorders are thought to originate from altered release of melatonin. Many factors can impair its release including exposure to artificial light at night. Light pollution, more common in urban areas, comprises some of the artificial light at night affecting sleep quality. The goal of our project was to assess the possible correlation between the rate of ASD individuals with or without a diagnosed sleep disorder and the level of light pollution in neighborhoods of large metropolitan areas and cities in rural regions of Southern California. The cities examined were grouped by county and the Bortle Dark-Sky Scale, which rates the amount of light pollution present at night. First, using the UCLA i2b2 Center records, which includes patients that received care at UCLA Health affiliated hospitals and clinics, we determined the number of patients with a diagnosis of ASD or of a sleep disorder. Then the difference in the percentage of patients with ASD, sleep disorders, and both was compared in cities with low light pollution versus those with a high one to evaluate if light pollution at night has an influence on the rates of individuals with ASD who also have sleep disorders. Our findings suggest that the ASD population presents with a significantly higher rate of sleep disorders compared to the general population across all counties in Southern California. Furthermore, rural areas with low levels of light pollution did have lower rates of sleeping disorders than areas with moderate to high levels of light pollution. However, rural areas did not show significantly lower rates of sleeping disorders among patients with ASD. The rates of individuals with ASD, or with ASD plus sleep disorders did not vary significantly among counties and cities, nor did they seem to be correlated with levels of light pollution. Overall, our findings suggest that individuals with ASD are more likely to present with altered sleep/wake cycles. The level of light pollution may play a role in sleep disorders but there are other factors at play.

Disclosures: D.S. Bhandal: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; HRSA. **J.B. Tuschhoff:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; HRSA. **D.M. Davies:** B.

Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; HRSA. **K. Nguyen-Ngo:** None. **C.S. Colwell:** None. **C.A. Ghiani:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.16/A31

Topic: A.07. Developmental Disorders

Support: NIH 1 R03 MH127401-01

Title: Temporal pattern of developing memory deficit in Shank3 mouse model of autism

Authors: *N. SHI[1], S. VICENCIO[2], A. M. LAUER[2], T. DEEMYAD[2];
[1]Otolaryngology, Johns Hopkins Med., Baltimore, MD; [2]Otolaryngology-HNS, Johns Hopkins Univ., Baltimore, MD

Abstract: Temporal Pattern of Memory Deficit Development in Shank3 Mouse Model of Autism Nelson Shi, Sergio Vicencio, Amanda Lauer, and Tara Deemyad
Recent studies suggest a link between autism spectrum disorders (ASD) and Alzheimer's disease (AD), notably in memory impairments. Approximately 10% of individuals diagnosed with autism in their 40s to 60s may develop dementia within 15 years. AD impacts multiple memory systems including episodic memory, which is also commonly impaired in autism. These memory deficits are typically seen at older ages in neurotypical individuals. The onset and progression of memory deficits in those with ASD, however, remain poorly understood.
In this study, we used memory-related rodent behavioral tasks to monitor the progression of cognitive function in episodic, spatial working, and associative memories in a mouse model with a SHANK3b mutation ($SHANK3b^{-/-}$), a leading gene implicated in ASD, relative to control mice. The groups are categorized by sex and age: 3-4 months, 7-8 months, and 12 months. These ages correspond to approximately 20-23, 32-34, and 40 human years, respectively. We identified episodic memory deficits in mice. Shank3b knockout mice exhibited reduced performance in a novel object recognition test as early as 4-6 months of age, earlier than what has been previously reported. This memory impairment becomes more pronounced by the age of 7 months. Furthermore, male mice demonstrated relatively lower discrimination scores, suggesting that this deficit may affect male mice more severely than female mice.
During the behavioral tasks, one-photon calcium imaging of neurons and astrocytes in anterior cingulate cortex will be performed. The ability to record from neurons and astrocytes in freely moving animals provides a platform for developing and testing hypotheses of neural circuit mechanisms responsible for memory decline in ASD.

Disclosures: N. Shi: None. **S. Vicencio:** None. **A.M. Lauer:** None. **T. Deemyad:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

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Program #/Poster #: PSTR434.17/A32

Topic: A.07. Developmental Disorders

Support: NIMH R01MH124808
The Jakob Gene Fund
NICHD P50HD103525

Title: Temporal restriction of neurodevelopmental disorder associated gene MYT1L to identify potential windows for interventions.

Authors: *K. MCCULLOUGH[1], S. E. MALONEY[2], J. D. DOUGHERTY[3];
[1]Genet., Washington Univ. In St. Louis, Saint Louis, MO; [2]Psychiatry, Washington Univ. Med. Sch., Saint Louis, MO; [3]Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Temporal restriction of neurodevelopmental disorder associated gene MYT1L to identify potential windows for interventions. Katherine B. McCullough[2,3], Susan E. Maloney[1,2] , Joseph D. Dougherty[1,2,3] [1]IDDRC, Depts. of [2]Psychiatry, [3]Genetics, at Washington University School of Medicine St. Louis, MO, USA.
Putative loss of function mutations in the MTY1L gene lead to the newly defined intellectual and developmental MYT1L Syndrome characterized by global developmental, motor and speech delay, intellectual disability, highly penetrant obesity and hypotonia, and a significant subset with autism spectrum disorder and/or attention-deficit/hyperactivity disorder. How MYT1L loss of function mutations result in disease is poorly understood. We developed the first MYT1L haploinsufficient mouse model, which recapitulates many patient phenotypes, including hyperactivity, changes in communicative behavior, social behavior challenges, motor disruptions, hypotonia, and microcephaly. We identified disrupted gene expression, precocious neuronal differentiation, and failure of transcriptional and chromatin maturation in adults. It is unknown when during development the disruption of MYT1L protein leads to each specific clinically-relevant phenotype. To identify therapeutic approaches, we need to determine whether the absence of MYT1L affects neurodevelopment during embryonic stages, postnatal or adult phases. To begin to address this, we recently generated a MYT1L conditional model targeting the same exon as our constitutive haploinsufficient model to allow for spatial and temporal restriction of MYT1L loss. We leveraged this model and inducible Cre-recombinase tools to induce loss of MYT1L in the postnatal brain, after completion of early neurodevelopment, to determine which phenotypes are due to the postnatal functions of MYT1L. Deletion of MYT1L at P30, an age after most of neurodevelopment has completed, did not result in similar behavioral phenotypes to those observed in our constitutive deletion model. These results suggest that loss of MYT1L alters the development of the circuits meditating these phenotypes. Targeting these circuits or direct MYT1L targets will likely be a more successful intervention strategy than directly increasing MYT1L activity through gene therapy approaches.Funding Support: The

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Disclosures: K. McCullough: None. **S.E. Maloney:** None. **J.D. Dougherty:** None.

Poster

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Program #/Poster #: PSTR434.18/A33

Topic: A.07. Developmental Disorders

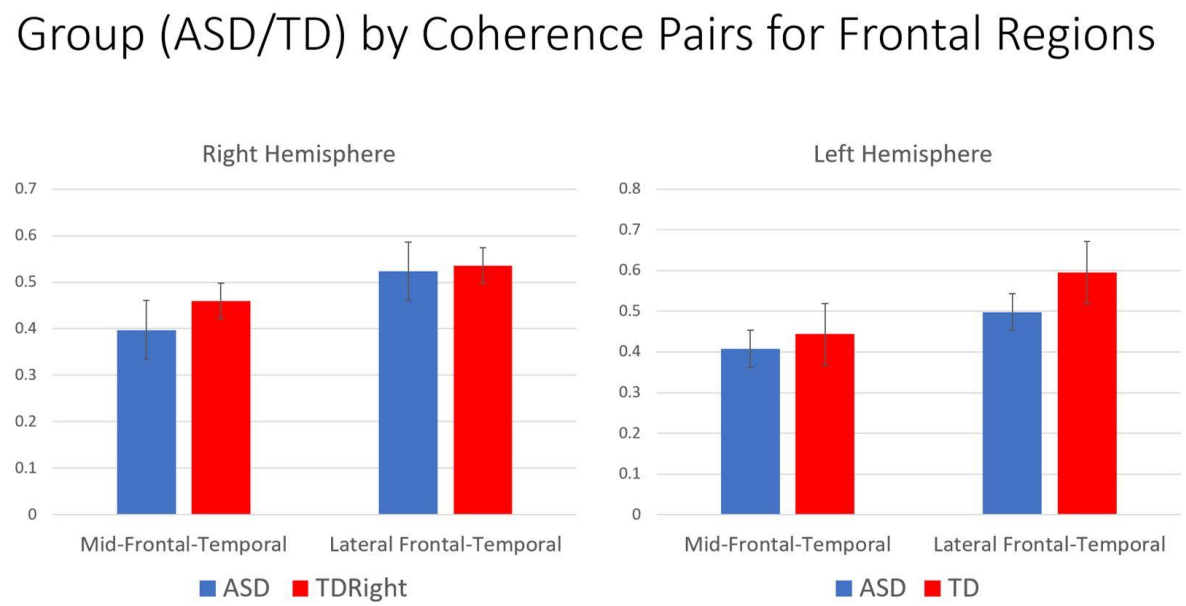
Support: Neuroscience Pilot Grant 2021

Title: Alpha-frequency functional coherence and facial emotion recognition in asd children

Authors: *K. BROOKS[1], **L. VIALE**[2], H. CABAN[3], N. A. SHANOK[4], K. D. MIZE[6], N. JONES[5];
[1]Florida Atlantic Univ., Delray Beach, FL; [2]Psychology, Florida Atlantic Univ., Deerfield Beach, FL; [3]Psychology, Florida Atlantic Univ., Pembroke Pines, FL; [4]Florida Atlantic Univ., Boca Raton, FL; [5]Psychology, Florida Atlantic Univ., Jupiter, FL; [6]Psychology, Florida Gulf Coast Univ., Fort Myers, FL

Abstract: Facial emotion recognition is a crucial component of social communication, and it is markedly seen as a deficit among children diagnosed with autism spectrum disorder (ASD). The brain's functional coherence is thought to be associated with facial emotion recognition and social communication abilities in general. This study investigates the relationship between autism symptom severity and facial emotion recognition abilities by comparing an autistic and typically-developing group in their performance of a standardized task. Across three studies, 74 children between 4-8 years old participated. Researchers gave participants a computerized task assessing their ability to recognize the facial emotion displayed from a collection of images. The facial stimuli expressed emotions including happiness, sadness, anger, and fear. Results showed that children diagnosed with autism performed with less accuracy in the facial emotion recognition task in comparison to typically developing children $F=(1, 68) = 10.78$ $p=.002$. In addition, alpha-band frequency EEG coherence readings were obtained in frontal to occipital sites (6 pairs in each hemisphere). Results showed that the children in the autistic group had a pattern of lower alpha-frequency functional coherence in anterior regions compared to children in the typically developing group $F=(5, 35)= 2.65$ $p=.04$. Lower alpha-frequency frontal and temporal functional coherence in children diagnosed with autism is indirectly associated with social brain development. These results support the hypothesis that hindered facial emotion recognition is a characteristic symptom of ASD, and it suggests that these difficulties stem from higher variance in postnatal brain development in areas responsible for developing social-emotional skills. Such findings emphasize the need for early identification of autism and early

intervention methods so that children can develop better facial emotion recognition and, overall, improve their social communication abilities.



Disclosures: K. Brooks: None. **L. Viale:** None. **H. Caban:** None. **N.A. Shanok:** None. **K.D. Mize:** None. **N. Jones:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.19/A34

Topic: A.07. Developmental Disorders

Title: Fnirs-related patterns of cortical activation in children with autism spectrum disorder (asd)during a whole body coordination and executive functioning task

Authors: *J.-M. TSAI[1,2], J. COREY[1], S. KATHIRAVAN[3], L. ALEXANDER[4], A. BHAT[1]; [1]Physical therapy, [2]Interdisciplinary Neurosci. Grad. program, Physical therapy, [3]Univ. of Delaware, Newark, DE; [4]Univ. of Delaware, New Castle, DE

Abstract: Children with Autism Spectrum Disorder (ASD) have significant co-occurring impairments in motor and cognitive functioning (Bhat, 2020; Demetriou et al., 2018). However, few studies have examined the underlying cortical mechanisms (Mostofsky et al., 2006; Wymbs et al., 2021). In the current study, we compared cortical activation during a motor and a cognitive task with two conditions. 24 children with and without ASD between 6 and 17 years of age completed a whole-body march-tap task and a Flanker task while collecting functional near-infrared spectroscopy (fNIRS) data. The march-tap tasks involved 2 conditions (a) Contralateral

knee-tapping (b) Ipsilateral knee-tapping. The Flanker test involved two conditions (a) Congruent (b) Incongruent (the central stimuli was opposite the to the outward stimuli). The fNIRS oxy-hemoglobin signal was further analyzed using t-test to study differences in activation patterns between task conditions for each task, between right and left hemispheres, in various ROIs- prefrontal (MFG), inferior frontal (IFG), superior temporal (STS), precentral (PCG) and inferior parietal regions (IPL). Preliminary data of the 6 children [age= 13.6 (0.91), all male] suggests greater activation in left STS (83% participants), left PCG, right STS, left/right IPL (67% participants) during contralateral tapping vs. ipsilateral. It also suggested lower left IPL (83% participants) and greater left MFG, right STS, IFG, PCG (67%) activation during incongruent vs. congruent trials. Further correlations between cortical activation and behavioral performance, and comparisons between children with/without ASD will be conducted. Conclusions: Differences in cortical activation across the motor and cognitive task conditions between children with and without ASD will help explain the differing cortical contributions in autistic individuals compared to non-autistic individuals when performing motor and cognitive tasks. In terms of intervention implications, we propose using fNIRS-based biomarkers to track changes in motor and cognitive performance following motor/EF-based exercise interventions.

Disclosures: J. Tsai: None. **J. Corey:** None. **S. Kathiravan:** None. **L. Alexander:** None. **A. Bhat:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.20/A35

Topic: A.07. Developmental Disorders

Support: Conahcyt Mexico Fellowship 761616 (SZE)
Coveicydet Grant 1011 2023/2023 (MSAA)

Title: Long-term changes in attention stimulated by a robot in children with autism wandering in an open field setting

Authors: S. ZEPEDA ESQUIVEL[1], *M. HERNANDEZ[1], R. TOLEDO-CARDENAS[1], M. ALEJANDRE APOLINAR[2], H. AMORES PÉREZ[2], I.-A. GARCIA-GONZALEZ[2], D. HERRERA-COVARRUBIAS[1], G. A. CORIA-AVILA[3], **J. MANZO**[4];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by challenges in social communication, restricted interests and repetitive behaviors. Moreover, individuals with ASD often struggle to maintain attention on tasks, becoming easily distracted by other stimuli. In a previous study, we engaged children with ASD in virtual sports within a

controlled indoor environment. Alongside our data, we observed that initially, these children exhibited random movement throughout the room. However, with repeated exposure to the stimulation, they demonstrated a tendency to concentrate their movement within specific areas, mirroring the behavior of neurotypical children. This observation prompted an exploration into the walking patterns of ASD children in an open field setting. Open field studies are a well-established method in laboratory animals, facilitating the observation of movement, exploratory behavior, interactions, and responses to various stimuli within an enclosed space. Thus, a bespoke open field setting was constructed at the Institute of Technology of Xalapa, Veracruz, Mexico, designed to capture the movement of children within the room. The room featured an entrance/exit door, two windows, and minimal furnishings, with a designated area for a robot. A cohort of 12 neurotypical and 12 ASD children participated in the study. Each child entered the room twice a week over eight months, 20 min each session. In each session, the robot performed seven distinct actions, while the position of the child's head was recorded at five-second intervals. Results revealed that neurotypical children consistently directed their attention towards the robot from the outset, confining their movement to specific areas within the room. In contrast, ASD children initially displayed reduced attention towards the robot and traversed a significantly larger area. However, after approximately 3-5 months, a notable shift occurred in the behavior of children with ASD. They began to exhibit movement patterns and attentional focus akin to their neurotypical counterparts. These findings suggest that repetitive exposure to a consistent stimulus can mitigate attentional challenges in children with ASD. Although the neurological implications of this attentional shift remain unclear, our study propose an effective strategy for enhancing attention through repetitive environmental stimulation, with potential applications for learning and social interactions.

Disclosures: S. Zepeda Esquivel: None. **M. Hernandez:** None. **R. Toledo-Cardenas:** None. **M. Alejandre Apolinar:** None. **H. Amores Pérez:** None. **I. Garcia-Gonzalez:** None. **D. Herrera-Covarrubias:** None. **G.A. Coria-Avila:** None. **J. Manzo:** None.

Poster

PSTR434: Neurodevelopmental Disorders and Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR434.21/A36

Topic: A.07. Developmental Disorders

Title: A framework for investigating sensory integration in marmosets

Authors: *A. B. FATH[1,2], J. ESSEMIAH[3], K. BELIARD[3], F. LIANG[3], W. MENEGAS[3], Q. ZHANG[3], G. FENG[1];
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Abstract: Atypical sensory processing has been observed across several neurodevelopmental disorders, yet the behavioral and neural mechanisms underlying this deficit remain poorly understood. More specifically, such sensory deficits have been observed across several sensory modalities and have been especially well documented in humans when perceptual judgments require the accumulation and integration of sensory information over time. The study of sensory alterations in rodent models of neurodevelopmental disorders have produced variable results and are limited in their ability to accurately reflect human conditions and predict outcomes. Non-human primate, marmoset, models of neurodevelopmental disorders, such as autism spectrum disorder (ASD), have recently been developed, which allow for a unique opportunity to better understand the complex behavioral and neural processes underlying sensory processing in neurodevelopmental disorders. In this study, we propose a framework to study sensory processing in marmosets. We implemented a free response version of a pulse based sensory evidence accumulation task originally developed in rats, and use pose estimation along computational models to quantify and understand the process of sensory integration. The task presents sensory information in a sequence of flashes on the left and right sides of a screen, while freely moving marmosets must choose the side with higher flash probability to receive a reward. The task presents a speed-accuracy tradeoff, in which longer response times result in a greater probability of choosing the correct side, as it allows the marmoset to sample more sensory (flash) evidence. We hope this framework will provide a foundation for studying sensory processing deficits across marmoset models of neurodevelopmental disorders in the future.

Disclosures: A.B. Fath: None. **J. Essemiah:** None. **K. Beliard:** None. **F. Liang:** None. **W. Menegas:** None. **Q. Zhang:** None. **G. Feng:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.01/A37

Topic: A.07. Developmental Disorders

Support: the National Key Research and Development Program of China (2021ZD0202500)

Title: Autistic-like behavior and cerebellar ataxia in Purkinje cell Bcl11a knock-out mice

Authors: *Y.-C. YU;
Fudan Univ., Shanghai, China

Abstract: The *BCL11a* gene encodes a transcriptional factor with essential functions in brain development. Pathogenic variants of the *BCL11a* gene cause an intellectual developmental disorder, also known as Dias-Logan syndrome (DLS), in humans, manifesting as intellectual disability, autism spectrum disorder, postnatal microcephaly, hypotonia, and behavioral abnormalities. Although recent studies in DLS patients demonstrate cerebellar pathology, to date,

BCL11a's roles and the sequelae of BCL11a dysfunction in the cerebellum have not been investigated. Using single-nuclei RNA sequencing (snRNA-seq) and immunostaining, we found that BCL11a is exclusively expressed in cerebellar Purkinje cells (PCs). To explore the potential roles of BCL11a in cerebellar PCs, we crossed BCL11a$^{F/F}$ mice with Pcp-Cre mice. We found that specific ablation of BCL11a in PCs significantly reduces the cerebellar volume, the number of PCs, and the thickness of the molecular layer. Moreover, *BCL11a* conditional knockout (cKO) mice exhibit social impairments and cerebellar ataxia, consistent with clinical observations in DLS patients. Mechanistically, deletion of BCL11a results in smaller soma sizes of PCs, as well as reduced dendritic arborization and spine density. Furthermore, electrophysiological recordings showed that *BCL11a* cKO does not affect the inhibitory synaptic inputs of PCs, but significantly reduces their excitability and excitatory synaptic inputs. Additionally, analysis of snRNA-seq, immunostaining and Western blot data indicates that the expression of Rho guanosine nucleotide exchange factor 3 (Vav3) in PCs is significantly reduced in *BCL11a*-cKO mice. Importantly, genetic overexpression of Vav3 in PCs can partially rescue synaptic and behavioral phenotypes in *BCL11a*-cKO mice. Together, these findings demonstrate novel roles for BCL11a in PC function and provide a potential therapeutic strategy for DLS.

Disclosures: Y. Yu: None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.02/A38

Topic: A.07. Developmental Disorders

Support: 1ZIANS002994-21

Title: Neurodevelopmental disorder-associated variants affect NMDA receptor signaling and trafficking

Authors: *H. RYU[1], S. LEE[1], M. M. VIEIRA[4,2], K. W. ROCHE[3];
[2]Natl. Inst. of Neurolog. Disorders and Stroke, [3]RBS/NINDS, [1]NIH, Bethesda, MD; [4]NINDS, Building 35, Bethesda, MD

Abstract: Neurodevelopmental disorder-associated variants affect NMDA receptor signaling and trafficking

Hye Young Ryu[1], Saerom Lee[1], Marta Vieira[1], Shuxi Li [2], and Katherine W. Roche[11] Receptor Biology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892 [2] Clinical Genetics Department, GeneDx, 207 Perry Parkway, Gaithersburg, MD 20877

Rare variants in synaptic proteins are implicated in various neurodevelopmental disorders (NDDs), including autism spectrum disorders (ASDs), intellectual disability, and epilepsy. Genes encoding NMDA receptors (GRIN genes) are highly associated with NDDs, and a growing

number of people are being diagnosed with GRIN disorders. We have focused on variants located in the C-terminal domain (CTD) of NMDA receptors, which is a finely modulated region of NMDARs important for mechanisms of trafficking of NMDARs and anchoring at synaptic sites. We are studying two rare GRIN2B variants within the C-terminal domain (CTD) identified from human patients: GluN2B-1485 CextX1 (1aa extension) and GluN2B-1485 CextX7 (7aa extension) in patients with intellectual disability and epilepsy. Our results indicate that both extension variants exhibit reduced targeting to the cell surface and decreased interaction with SAP102 and PSD-95. Furthermore, the proteins were destabilized. Through our work, we discovered a selective degradation pathway for GluN2B. We performed a comparative analysis between proteasomal and lysosomal degradation specific inhibitors (eg. MG-132 for the proteasomal pathway and chloroquine for the lysosomal pathway). The protein stability of the extension variants was selectively rescued by the lysosomal inhibitor, chloroquine. These data provide valuable insight into the mechanisms that maintain GluN2B stability and turnover. Our current work is focused on characterizing the effects of the GluN2B extension variants in relevant neuronal models, such as induced pluripotent stem cell (iPSC)-derived neurons. This comprehensive approach allows for a broader exploration of the intricate mechanism underlying NDDs associated with GRIN variants and offers valuable insights for future therapeutic strategies.

Disclosures: H. Ryu: None. **S. Lee:** None. **M.M. Vieira:** None. **K.W. Roche:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.03/A39

Topic: A.07. Developmental Disorders

Support: NIMH Grant MH113948
Civitan International Research Center Emerging Scholar Award

Title: Autism Risk Gene Cul3 Alters Neuronal Morphology via Caspase-3 Activity in Mouse Hippocampal Neurons

Authors: *Q. XIA[1], A. SINGH[1], J. WANG[1], Z. XUAN[1], J. D. SINGER[2], C. M. POWELL[1]; [1]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Biol., Portland State Univ., Portland, OR

Abstract: Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders (NDDs) in which children display differences in social interaction/communication and repetitive stereotyped behaviors along with variable associated features. *Cul3*, a gene linked to ASD, encodes CUL3 (CULLIN-3), a protein that serves as a key component of a ubiquitin ligase complex with unclear function in neurons. *Cul3* homozygous deletion in mice is embryonic lethal; thus, we examine the role of *Cul3* deletion in early synapse development and neuronal

morphology in hippocampal primary neuronal cultures. Homozygous deletion of *Cul3* significantly decreased dendritic complexity and dendritic length, as well as axon formation. Synaptic spine density significantly increased, mainly in thin and stubby spines along with decreased average spine volume in *Cul3* knockouts. Both heterozygous and homozygous knockout of *Cul3* caused significant reductions in the density and colocalization of gephyrin/vGAT puncta, providing evidence of decreased inhibitory synapse number, while excitatory synaptic puncta vGulT1/PSD95 density remained unchanged. Based on previous studies implicating elevated caspase-3 after *Cul3* deletion, we demonstrated increased caspase-3 in our neuronal cultures and decreased neuronal cell viability. We then examined the efficacy of the caspase-3 inhibitor Z-DEVD-FMK to rescue the decrease in neuronal cell viability, demonstrating reversal of the cell viability phenotype with caspase-3 inhibition. Studies have also implicated caspase-3 in neuronal morphological changes. We found that caspase-3 inhibition largely reversed the dendrite, axon, and spine morphological changes along with the inhibitory synaptic puncta changes. Overall, these data provide additional evidence that *Cul3* regulates the formation or maintenance of cell morphology, GABAergic synaptic puncta, and neuronal viability in developing hippocampal neurons in culture.

Disclosures: Q. Xia: None. **A. Singh:** None. **J. Wang:** None. **Z. Xuan:** None. **J.D. Singer:** None. **C.M. Powell:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.04/A40

Topic: A.07. Developmental Disorders

Support: NIH P30ES030283

Title: Expression of aquaporin-4 is altered in the cerebellum of a mouse model of autism

Authors: R. JAGADAPILLAI[1], A. IKRAM[3], *E. GOZAL[4], G. N. BARNES[2];
[1]Pediatric Res. Inst., [2]Dept Neurol, Univ. of Louisville Sch. of Med., Louisville, KY; [4]Dept of Pediatrics PRI /, [3]Univ. of Louisville, Louisville, KY

Abstract: Astrocytes, the most abundant glial cell type, account for one third of brain mass, and are involved in maintenance of the blood-brain barrier (BBB), regulation of water and nutrient support ion homeostasis, neurotransmitter metabolism, neuronal energy and importantly synaptic pruning. These functions are essential for normal brain function during early neurodevelopment and throughout life. Altered expression of astroglia markers, such as GFAP, aquaporin-4 (AQP4), connexin 43 (Cx43) have been reported in postmortem studies of autistic (ASD) patients. AQP4, expressed in astrocyte terminal feet that surround BBB blood vessels, is the most abundant water channel in the CNS and has an important role in cell migration. Cx43, an astrocytic gap junction protein regulates cellular growth, cell-cell adhesion, intercellular

communication, cell death, proliferation, and differentiation. Along with its role in motor control, the cerebellum also plays an important role in cognitive function by interconnecting with other brain regions. Evidence from human and pre-clinical models of ASD suggests that the cerebellum affects cognition and social behavior. Altered cerebellar astroglia AQP4 expression may indicate compromised cell structure, volume, ionic homeostasis, and synaptic pruning during development and throughout life contributing to brain abnormalities that could promote the appearance of autistic behaviors. Decreased AQP4, has been shown to compromise glutamate transporters and clearance from intercellular spaces, thereby exacerbating glutamate toxicity. These events can also facilitate harmful effects of aggravating neuro-inflammation, edematous condition, and impaired synaptic pruning as exhibited in ASD. We investigated whether cerebellar AQP4, Cx43, GFAP expression and co-localizations are altered in a BTBR mouse ASD model, using immunofluorescent staining and western blotting analysis in support of our cerebellum proteomics findings. Our data show that AQP4 significantly decreased in the BTBR cerebellum, compared to C57 mice. Moreover, cerebellar Cx43 and GFAP expression increased significantly in BTBR compared to C57 mice. In addition, we show higher colocalization of AQP4 and Cx43 with GFAP in BTBR cerebellum compared to C57 mice. Abnormal astrocytic signaling in BTBR mouse cerebellum may explain defects in sensory, motor, and cognitive processing in ASD subjects. Understanding the effects of astrocytes and their altered cerebellar GFAP, AQP4 and Cx43 signaling may allow the development of novel targeted therapeutics alleviating ASD patients' symptoms.

Disclosures: R. Jagadapillai: None. **A. Ikram:** None. **E. Gozal:** None. **G.N. Barnes:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.05/A41

Topic: A.07. Developmental Disorders

Support: SFARI SIMONS, FDN FSI00032

Title: The dynamic synaptic proteome of a developmental autism cohort

Authors: *R. RUIZ[1], M. L. MACDONALD[2];
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Autism is a developmental disorder with heterogenous genetic and environmental etiologies. Genetic risk in autism often converges on synaptic function. Synapses, due to their pivotal role in developmental circuit maturation, remain a primary focus of autism research, as consistent morphological abnormalities have been observed in both human and autism associated mouse models. Critically, the molecular pathways underlying synaptic anomalies in idiopathic autism remain elusive. To understand altered synapse maintenance, we compared whole cortex (Homogenate/Hom) and synaptic (Synaptosome/Syn) proteomes of primary visual cortex grey

matter from a developmental cohort of 31 autism and 31 neurotypical (NT) subjects. Pairs were aged 4-32, and matched for age, sex, race, and postmortem interval. This study represents the largest proteomic comparison of autism postmortem tissue to date, significantly examining both protein expression and synaptic localization throughout development. Using mass spectrometry, we quantified 4,727 proteins in Hom and 4,287 proteins in Syn. For the effect of diagnosis, 230 and 304 differentially expressed proteins (DEPs) ($q<0.1$) were identified in Hom and Syn, respectively. In autism subjects, the whole cortex (Hom) exhibited upregulation of cell adhesion and downregulation of voltage-gated channel subunits and mitochondrial electron transport chain proteins. Importantly, Hom DEPs were significantly enriched in differentially expressed transcripts identified in a largely nonoverlapping cohort. Fold change differences in synaptic protein levels by diagnosis were more pronounced than those in Hom, and they significantly deviated between tissue compartments. In contrast to Hom, local synaptic protein levels varied by diagnosis and age (n=305 DEPs). In early childhood, autism synaptosome enrichments had increased levels of synaptic vesicle cycling proteins, including the cortico-cortico excitatory marker *vGlut1*. Increased levels of mitochondrial cristae maintenance proteins suggest these synapses may be more active. These early childhood elevations were developmentally coregulated alongside reduced levels of numerous metabolic processes. These findings suggest a novel presynaptic mechanism of altered excitatory release in autism that is inversely developmentally coregulated with alterations in synaptic metabolism. Elucidation of these altered pathways, active during periods of atypical behavior, offer unique insights that inform future studies and age-specific therapeutic interventions.

Disclosures: R. Ruiz: None. **M.L. MacDonald:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.06/A42

Topic: A.07. Developmental Disorders

Support: National Brain Research Centre Core Fund

Title: Dendritic proteostasis and its implication in synaptic activity during autism

Authors: *S. SULTANA, S. SAMADDAR, S. BANERJEE;
Natl. Brain Res. Ctr., Manesar, India

Abstract: The etiology of Autism Spectrum Disorder (ASD) is attributed to the genetic heterogeneity and complex transcriptomic changes leading to profound deficits in neuronal development. Recent studies have demonstrated how such dysregulated gene expression patterns affect synaptic function and ASD-associated behavior; with several reports documenting how aberrant synaptic function could be a putative causality for ASD-related phenotypes. Regulation of the neuronal translatome, specifically the expression and modification of plasticity-related

proteins at the synapse; is emerging as an important focus of ASD-related research. For example, impairment of mTOR or ERK signaling, key regulators of translation, have been associated with autistic phenotypes. Despite the potential significance of translational regulation in ASD, our understanding of the mechanisms affecting the synthesis and degradation of the synaptic repertoire of proteins during the critical period of neuronal development in ASD is limited. In this study, we aim to determine the relationship between translation and post-translational modification of proteins during various stages of development in the synaptic compartment which contributes to the causality of ASD. We investigated the distribution of translation and proteasome machineries in the synaptic compartment and measured neuronal activity-dependent translation and proteasome activity in striatal and cerebellar synapses. The striatum and, more recently, the cerebellum are linked with many ASD phenotypes, and thus are the focus of our study. We have used two well-established rat models of ASD that include Fragile-X- Mental Retardation Protein (FMRP) and Neurexin1 (NRXN1) knockout rats to probe the involvement of *de novo* translation and protein degradation in ASD-associated deficits in synaptic activity. We have further analyzed the distribution and phosphorylation status of key translation factors; such as mTOR, ERK, ribosomal protein S6, and proteasome subunits; such as Rpt1, Rpt3, Rpt6 and the subunits of the 20S proteasome core at distinct developmental stages; such as juvenile (P21), adolescent (P42), and young adult (P70). To visualize the activity-dependent synaptic abundance of plasticity proteins, the study will evaluate the proteomic profile from striatal and cerebellar synapses using Mass Spectrometry (MS) analysis followed by puromycin labeling of newly synthesized proteins. The role of differentially expressed proteins in synaptic plasticity as identified by MS will be assessed by patch-clamp recordings from medium spiny neurons of the striatum and Purkinje neurons of the cerebellum.

Disclosures: S. Sultana: None. **S. Samaddar:** None. **S. Banerjee:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

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Program #/Poster #: PSTR435.07/A43

Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH111684
Duke Autism Center

Title: Examining proximity interactomes of autism genes to identify potential drivers of neurodevelopmental disorders

Authors: *N. MAXWELL[1], Y. GAO[2], E. J. SODERBLOM[3], S. H. SODERLING[1];
[1]Cell Biol., Duke Univ., Durham, NC; [2]Dept. of Neurosci., Baylor Col. of Med., Houston, TX;
[3]Duke Univ., Durham, NC

Abstract: Autism spectrum disorder (ASD) is a developmental disability with a complex genetic background. To date, 1140 genes have been implicated in autism susceptibility by the SFARI gene database. Proteins encoded by these genes cover a wide range of cellular functions and localizations, making it difficult to understand the mechanisms that drive ASD etiology. In this study, we utilize biotin-identification (BioID), a proximity based proteomic method that allows us to label and isolate proteins within a 10nm radius of a protein of interest, and identify these proteins using LC/MS. Our lab has developed a one-vector CRISPR/Cas9 Homology independent Universal Genome Engineering (HiUGE) approach, which allows for rapid, endogenous gene knock-in of a wide variety of payloads. With this technique, we are able to knock-in an engineered biotin ligase, TurboID, to identify the proximity-based proteomic interactomes of specific proteins of interest. We utilized this technique to study the interactomes of multiple ASD genes from the SFARI gene database with a broad goal of identifying potential common mechanisms or pathways that may be critical for the etiology of ASD phenotypes. We have previously identified the proteomes for 14 different ASD candidate genes that are critical for synapse development and function. Now, we have nearly doubled our targets, including genes that encode synaptic adhesion, signaling, and RNA binding proteins. The AlphaFold predicted structure of each protein is used to identify regions in each gene that are most likely to provide successful fusion proteins without disrupting endogenous function. We then utilize AAV transduction in Cas9-transgenic mice to knock-in TurboID to the gene of interest. Three weeks later, mice are treated with 5mM biotin for 5 days, then cortical brain tissue is removed, and proteins purified through a streptavidin pull-down prior to LC/MS analysis. Around 16% of the proteins identified in these interactomes are encoded by mouse orthologs of SFARI ASD genes. Additionally, a high number of these interactions are not identified within the STRING database. Each interactome also reveals a high number of proteins with functions related to the bait protein, suggesting a high degree of specificity within the dataset. With this approach, we are able to rapidly identify interactomes of ASD genes, providing new insights into their functions and a critical foundation for the discovery of central mechanisms that drive ASD.

Disclosures: N. Maxwell: None. **Y. Gao:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pending Patent on HiUGE technology. **E.J. Soderblom:** None. **S.H. Soderling:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pending Patent on HiUGE technology.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.08/A44

Topic: A.07. Developmental Disorders

Support: The Swedish Research Council
Adlerbertska stipendier
HE Ebbesdotter Mark-Järnberg

Title: Primary cilia morphological dynamics during hippocampal development

Authors: *S. RASMUSSON[1,2], S. JABBARI SHIADEH[2], P. SVEDIN[2], C. MALLARD[2], M. ARDALAN[2];
[1]Dept. of Physiol., Gothenburg University, Sahlgrenska Acad., Gothenburg, Sweden; [2]Dept. of Physiol., Sahlgrenska Academy, Univ. of Gothenburg, Gothenburg, Sweden

Abstract: The developing brain needs flexible neuronal circuits in order to adapt in response to theeverchanging environment. The primary cilium is an antenna-like structure that protrudes fromneurons and might regulate plasticity homeostasis by sending intracellular signals in responseto changes in extracellular compositions, influencing brain development. Abnormalities in cilialength or morphology can disrupt signaling pathways essential for proper brain developmentand neuronal circuit formation. These disruptions may lead to the characteristic behavioralabnormalities of neurodevelopmental disorders. Importantly, the developmental progression of the primary cilium remains incompletelyelucidated. Therefore, in this study, we investigated development of cilia including morphologyof cilia during brain development. We used wild type C57/Bl6 mice at the age of postnatal(P)12 (neonatal), and P45 (adolescent). Morphology of primary cilia as an indicator of ciliafunction was examined by 3D stereological analysis on stained hippocampal sections with anantibody to adenylyl cyclase III (ACIII), a specific marker of primary cilia. We found age-dependent cilia development in the hippocampus and that the cilia in theCA1P subregion were significantly different across the ages with longer cilia at P45 comparedto the P12. Regarding the subregional differences, at P12, length of cilia in the GCL neuronswere shorter than in the CA1.P and CA3.P. This difference was stronger between CA1.P andGCL than between CA3.P and GCL. At P45, apart from the difference in ciliary length betweenGCL and both CA1.P and CA3.P, there was also a difference between CA1.P and CA3.P. Our results suggest that the morphology of primary cilia in the hippocampus undergoes age-dependent changes during brain development, with variations in ciliary length observedbetween different subregions at different postnatal ages.

Disclosures: S. Rasmusson: None. **S. Jabbari Shiadeh:** None. **P. Svedin:** None. **C. Mallard:** None. **M. Ardalan:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.09/A45

Topic: A.07. Developmental Disorders

Title: Evaluation of diolistic labeled motor cortex neuronal morphology in a developmental hyperserotonemia rat model for autism spectrum disorder

Authors: *L. HOUGH[1], E. HOLLAND[2], L. STAUDT[1], C. DILLINGER[3];
[1]Kansas City Univ., Joplin, MO; [2]Neurosci., Univ. of Wisconsin, Madison, WI; [3]Chandler Regional Med. Ctr., Scottsdale, AZ.

Abstract: Developmental hyperserotonemia (DHS) is the most consistent neurochemical finding reported in autism and has been implicated in the pathogenesis of autism spectrum disorder (ASD). Accordingly, pre-and postnatal administration of the non-selective serotonin agonist, 5-methoxytptamine, has been hypothesized as a model of developmental hyperserotonemia to examine the behavioral and cytoarchitectural implications in ASD. Our previous investigations of the DHS model have demonstrated significant neurodevelopmental changes in the architecture, connectivity, and function of various areas of the motor system. While ASD is characterized by deficits in social cognition, disordered communication, restricted interests and repetitive behaviors, abnormalities in basic motor control, skilled motor gestures, and motor learning are commonly associated with the disorder. These motor disturbances may be linked to a possible defect in the pre- and postnatal development of specific neural networks including the dentate-thalamo-cortical pathway, which is involved in motor learning, automaticity of movements, and higher cognitive functions. This study presents a method to further analyze the morphology and connectivity of neurons located in the motor cortex of DHS animals. A modified diolistic labeling protocol was developed utilizing a Bio-Rad Helios chambered gene gun to label multiple tissue sections with lipophilic carbocyanine dyes. This method allows for efficient, reproducible visualization and analysis of motor cortex neuronal morphology. The use of lipophilic carbocyanine dyes, combined with particle- mediated biolistic delivery facilitates non-toxic fluorescent labeling of multiple neurons and dendritic arbors in fixed tissue. Confocal microscopy and 3-dimensional neuronal tracings were performed to asses neuronal morphology in the DHS and control populations.

Disclosures: L. Hough: None. **E. Holland:** None. **L. Staudt:** None. **C. Dillinger:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.10/A46

Topic: A.07. Developmental Disorders

Support: U.S army W81XWH-22-1-0536

Title: Involvement of amygdala neurons in male predominance of autism spectrum disorder

Authors: *N. MONTEFIORE[1,2], Y. YAROM[3,2];
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Abstract: Male predominance is one of the least understood characteristics of Autism Spectrum Disorder (ASD). While more than a hundred genes are involved in ASD, only a few of them

show sex differences in behavior. In previous work, we found that male mice harboring a mutation in the Pogz gene ($Pogz^{+/-}$) show sexually dimorphic overly friendly behavior in several sociability assays. Mapping the engaged neurons during social recognition revealed that in $Pogz^{+/-}$ males, there are more activated neurons in the basolateral amygdala (BLA) than in control and $Pogz^{+/-}$ female mice. To characterize the morphophysiological properties of these BLA neurons, we conducted in-vitro whole-cell recordings in acute brain slices from both $Pogz^{+/-}$ and control mice. We employ targeted recombination in active populations (Trap2) to label the neurons in response to a social smell test. Preliminary results from single-cell recording from the BLA present three types of principal neurons, characterized by unique AHP and spike train accommodation in response to a long current injection. Initial results also indicate that the neurons active during the social smell test exhibit characteristics similar to a specific subtype of the principal neurons we identified in the BLA. Further results are needed, and experiments are underway to collect more data. Another direction applied to identify the subtypes of principal neurons in the BLA, and to examine the correlation between $Pogz^{+/-}$ gene and the mice sex, is to characterize the morphology of the patch cells and the activated trapped cells. Our method includes labeling the recorded neuron and performing reconstruction analysis for the BLA neurons activating in a social smell test. This analysis will further expose any correlation between male predominance and overly friendly behavior and the basis of the properties of the neuronal network. Our results will pave the way to understanding the role of amygdala neurons in ASD model mice and advance our knowledge about autism spectrum disorder.

Disclosures: N. Montefiore: None. **Y. Yarom:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.11/A47

Topic: A.07. Developmental Disorders

Support: Hartwell Foundation through an Individual Biomedical Research Award A23-2439

Title: Linking layer 5 pyramidal neuron channelopathies to circuit E/I imbalances and neurodevelopmental disorders in a multiscale model of motor cortex

Authors: *M. LEITNER[1], R. BARAVALLE[1], J. CHEN[1], T. FENTON[2], R. BEN-SHALOM[3], S. DURA-BERNAL[1,4];
[1]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]Univ. of California Davis, Davis, CA; [3]Neurol., UC Davis Med. Ctr., Sacramento, CA; [4]The Nathan Kline Institute for Psychiatric Research, Orangeburg, NY

Abstract: A significant portion of the population is impacted by neurodevelopmental disorders (NDDs) such as epilepsy, autism spectrum disorder (ASD), and developmental delays. Although

these disorders exhibit significant clinical variability, they share common pathophysiological characteristics of imbalanced excitatory inhibitory (E/I) input. This imbalance arises during development, causing dysfunction in neuronal circuits resulting in atypical phenotypes. Brain channelopathies are a group of neurological disorders caused by mutations in ion channels and are commonly used to study E/I imbalance because their function can be linked to neuronal excitability. Channelopathies can cause an increase or decrease in the excitability of neurons, which can be a result of a change in the number of functional channels or channel biophysics. Channelopathies and disruption of neuronal activity are highly associated with NDDs. Layer 5 pyramidal neurons (L5PNs) have a high expression of NDD-associated genes and are particularly sensitive to E/I imbalance. L5PNs are the main output of cortical networks and have been shown to be a reliable marker for the excitability of the circuit as a whole, making them a valuable population to study. To investigate channelopathies in L5PNs, we utilize a published primary motor cortex (M1) model. Using this large-scale, highly detailed biophysical neuronal simulation, we can better understand how these channelopathies affect individual and network neuronal activity. These simulations can provide a mechanistic understanding of the role of channelopathies in E/I imbalance and how they contribute to NDD pathology. Using the M1 cortical column simulation, we measured how channel biophysical changes affect the overall excitability of the network and changes in neuronal population firing patterns to better understand the pathophysiology of the simulated channelopathy. We implemented specific gene mutations in ion channels highly associated with NDDs to study specific channelopathy cases and the resulting disruption in neuronal activity. We will also explore pharmacological interventions aimed at restoring the E/I imbalance disrupted by channelopathies to a neurotypical state. This will allow us to better understand therapeutic targets that specifically target disease symptoms and possibly unveil novel therapeutics that can be translated clinically.

Disclosures: M. Leitner: None. **R. Baravalle:** None. **J. Chen:** None. **T. Fenton:** None. **R. Ben-Shalom:** None. **S. Dura-Bernal:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.12/A48

Topic: A.07. Developmental Disorders

Title: Computational Biophysics of 2D Neuronal Network Dynamics in Cultures of KCNT1-Mutant Primary Neurons

Authors: *A. WEINER[1], R. BEN-SHALOM[2];
[1]Biomed. Engin., Univ. of California, Davis Chapter, Davis, CA; [2]Neurol., UC Davis Med. Ctr., Sacramento, CA

Abstract: Computational Biophysics of 2D Neuronal Network Dynamics in Cultures of KCNT1-MutantPrimary NeuronsAdam Weiner[1], Roy Ben-Shalom[1,2][1]Biomedical

Engineering Graduate Group, University of California, Davis; [2]UC Davis Health,Department of Neurology**Introduction.** High-density microelectrode arrays (HD-MEAs) are cutting-edge tools for studyingneuronal networks in vitro with high spatial and temporal resolution (Ballini et al., 2014; Obien et al.,2015). With thousands of electrodes, and each neuron spanning up to hundreds of electrodes, HD-MEAsallow detection subtle differences in extracellular electrical activity of neuronal cultures, making themideal for investigating genetic correlates of neurodevelopmental disorders where such differences arelinked to downstream cognition and behavior in animal models and human patients. Manyneurodevelopmental disorders, such as autism, intellectual developmental delay, and epilepsy, arecaused by dysfunction in neuronal excitability, inhibition, and neuroplasticity, with a significant number ofgenes implicated in such dysregulation (Satterstrom et al., 2020).**Materials and Methods.** We use HD-MEA devices with 26,400 platinum electrodes as described by(Ballini et al., 2014). We have experimental data describing neuronal network behavior of primaryneuronal cultures derived from cortices of genetically mutated mouse lines, each representing a specificgene associated with neurodevelopmental disorders. Among others, these genes include KCNT1,SYNGAP1, and SCN1A, which are implicated in various conditions such as autism spectrum disorder,intellectual disability, and epilepsy (Satterstrom et al., 2020).**Results.** We have begun development of computational models of neuronal networks using the NetPyNEframework (Dura-Bernal et al., 2019). Here we leveraged the spatiotemporally high-resolution dataobtained from HD-MEAs to create simulations of network activity on a virtual 2D-plane representing anHD-MEA environment. The models have been constrained by the spatial locations and connectivitypatterns of the identified putative neurons (IPNs) obtained from experimental data using modifiedmachine learning–assisted methods (Hornauer et al., 2024).

Disclosures: A. Weiner: None. **R. Ben-Shalom:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.13/A49

Topic: A.07. Developmental Disorders

Support: NIH NINDS R00NS089943

Title: Pipeline to unravel the impact of missense variants in protocadherin on cell-cell adhesion during synaptogenesis

Authors: *L. MAGANA HERNANDEZ[1], A. D. GUEMEZ-GAMBOA[2];
[1]Northwestern Univ., Chicago, IL; [2]Physiol., Northwestern Univ., Chicago, IL

Abstract: During development there are many processes that can go wrong which prevent the proper formation of the brain and nervous system. Cell adhesion is crucial for aiding the neuron to properly integrate into neural circuits. Protocadherins (PCDHs) are cell-cell adhesion

molecules, which form the largest subfamily of the cadherin family in vertebrates. PCDHs have a key role in the development of the nervous system through neurite outgrowth, synaptic differentiation & refinement, and later, synaptic maturation. Pathogenic variants in PCDHs have been associated with neurodevelopmental diseases such as autism spectrum disorder, seizures, microcephaly, epilepsy, etc. However, how these variants affect PCDH function, particularly cell-cell adhesion, is yet to be determined. I hypothesize that disrupted PCDH-mediated cell adhesion results in synaptogenesis defects. At present, I am involved in characterizing missense variants linked to neurodevelopmental disorders and developing a pipeline for their curation, focusing on the adhesive extracellular domain. In a pilot study, I have identified two missense variants that did not affect stability or localization but disrupted adhesion. Therefore, I am establishing iPSC lines carrying selected variants that disrupt PCDH-mediated adhesion by implementing CRISPR/Cas9 editing. I will use these lines to generate neurons for the assessment of synaptogenesis. My strategy involves subjecting the remaining PCDH hits to this pipeline and evaluating whether PCDH-mediated adhesion is similarly compromised. Understanding how variants affect PCDH function will provide insight into the mechanisms by which neurodevelopmental diseases arise and set the ground for potential therapeutic approaches.

Disclosures: L. Magana Hernandez: None. **A.D. Guemez-Gamboa:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.14/A50

Topic: A.07. Developmental Disorders

Title: Cortical Morphometry Comparison In Developmental Disabilities Compared To Typical Individuals

Authors: *M. MAHMOUDI[1], L. MOORE[2], J. LUNDQUIST[1], A. HOUGHTON[1], R. MCCOLLUM[3], K. B. WELDON[3], E. EARL[4], O. MIRANDA-DOMINGUEZ[1], B. TERVO-CLEMMENS[1], D. A. FAIR[2], E. FECZKO[5];
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Abstract: Understanding the neurobiological underpinnings of developmental disabilities is crucial for tailored interventions. However, large-scale studies often face methodological variability and lack clinical outcome enrichment, e.g., ABCD studies. To address this, we aggregated data from six datasets, including HBN, ABIDE I, ABIDE II, ABCD, OHSU ADHD, and OHSU ASD, and processed them uniformly using the ABCD-HCP pipeline. Cortical thickness, surface, and sulcal depth were parcellated using the HCP template. NeuroCombat was employed to harmonize multi-site datasets, mitigating batch effects.The two-way ANOVA with the main effect of the diagnostic group revealed significant variations in F-values and effect sizes

across different measurements and groups, including autism, ADHD, control, and clinical diagnosis. While differences were observed in cortical morphology across various ROIs and groups, significant differences between autism and all other groups were found only in the right-side 47s and 6mp ROIs.This underscores the importance of focusing on specific brain regions to enhance our understanding of the neurobiological basis of autism.

Disclosures: M. Mahmoudi: None. **L. Moore:** None. **J. Lundquist:** None. **A. Houghton:** None. **R. McCollum:** None. **K.B. Weldon:** None. **E. Earl:** None. **O. Miranda-Dominguez:** None. **B. Tervo-Clemmens:** None. **D.A. Fair:** None. **E. Feczko:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.15/Web Only

Topic: A.07. Developmental Disorders

Support: 22K07611
22K06440

Title: Postnatal IL-17A mRNA Dynamics in the Cerebral Cortex and Alterations in ASD Animal Models

Authors: *T. SASAKI[1], S. KAMIYA[1], K. NAKAMURA[1], K. HIGUCHI[1], K. KISHI[1], S. IWATA[2], Y. TAKEI[2];
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Abstract: Recent research underscores the involvement of immune modulation in the pathology of psychiatric disorders, including autism spectrum disorder (ASD). This study explores the role of T helper 17 (Th17) cells, producers of interleukin-17A (IL-17A), known for their role in inflammatory responses and autoimmune diseases. Focusing on IL-17A receptors IL-17RA and IL-17RC in the developing mouse brain, we utilized adult C57BL/6J mice in a maternal immune activation (MIA) model, employing poly(I:C) at gestational day 12.5. *in situ* hybridization (ISH) assessed *IL-17RA* and *IL-17RC* mRNA expression at various developmental stages, complemented by immunohistochemical staining to identify expressing cell types. Findings revealed differential expression patterns of *IL-17RA* and *IL-17RC* in cortical neurons, microglia, and astrocytes, with *IL-17RA* predominantly expressed in cortical layers V-VI during early development and notably down-regulated in the ASD model of MIA. This suggests a critical role during early cortical development, while *IL-17RC* showed a broader distribution without significant changes in the autism model. The expression of IL-17 receptors in the CNS, particularly during key developmental stages, underscores their potential impact on neurodevelopmental processes and points to a disrupted inflammatory response potentially contributing to ASD pathology. Our study provides novel insights into neuroimmune interactions in ASD, emphasizing the importance of IL-17A signaling pathways in the CNS. Future work will

investigate the direct effects of IL-17A on cortical morphogenesis to further elucidate its role in developmental disorders.

Disclosures: T. Sasaki: None. **S. Kamiya:** None. **K. Nakamura:** None. **K. Higuchi:** None. **K. Kishi:** None. **S. Iwata:** None. **Y. Takei:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.16/A51

Topic: A.07. Developmental Disorders

Support: OUHSC, Department of Neurosurgery

Title: Hippocampal network dysfunction in Cntnap2 knockout mouse model of autism spectrum disorder.

Authors: *H. FAIRCHILD[1], R. YELAHANKA NAGARAJA[2], R. PATERNO[3];
[1]Dept. of Neurosurg., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [2]Dept. of Cell Biol., Col. of Med., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [3]Neurosci. Program, Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: Contactin-associated protein-like 2 (CNTNAP2) gene mutations are associated to neurodevelopmental disorders, including autism spectrum disorder (ASD). Our recent studies have shown that Cntnap2 knockout (KO) animals exhibit a loss of parvalbumin (PV)+ interneurons, decreased perisomatic inhibition in hippocampal area CA1, as well as a complex disruption of theta-gamma oscillations along CA1 and reduced sharp wave ripple power (Paterno et al. Cell Rep. 2021). Derived from a subpallial region called the embryonic medial ganglionic eminence (MGE), PV+ interneurons (INs) provide a source of inhibitory synaptic input and play a pivotal role in coordinating ensembles of hippocampal pyramidal neurons. Although disruptions in PV+ INs and inhibitory synaptic changes are known to occur in ASD, how these hippocampal cellular changes lead to cognitive impairments in autism is largely unknown. Here, we aim to determine how changes in PV-positive interneurons impact CA1 principal cell networks in Cntnap2 KO mice. We recorded CA1 neuronal population dynamics and network activity using high-density silicon probes, along with monitoring animals' movements during hippocampal-dependent behavioral tasks. Recordings were performed while the animals were navigating an open field, a linear track, a delayed spatial alternation task, as well as during sleep states in the home cage before and after task performance. We measured pyramidal cells features, place field stability as well as place cell ability to remap in a new environment. Furthermore, we identified CA1 putative interneurons classified as PV interneurons and analyzed firing properties and correlation with theta phase. We found that CA1 pyramidal cells showed a reduced spatial information score in Cntnap2 KO compared to WT mice. Furthermore, sharp wave ripples did not exhibit increased power or frequency during non-REM sleep after

behavioral exposure. Our findings suggest that altered hippocampal circuit dynamics play a role in the autism phenotype.

Disclosures: H. Fairchild: None. **R. Yelahanka Nagaraja:** None. **R. Paterno:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.17/A52

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 MH097949-01
Autism Speaks Pilot Grant 7359

Title: Pten activity affected by subcellular localization

Authors: *N. DESMET[1], M. PRINA[3], A. ABDULKAREEM[2], B. W. LUIKART[4];
[1]Geisel Sch. of Med., Dartmouth Col., Hanover, NH; [2]Dartmouth Col., Lebanon, NH, ; [3]Univ. of Alabama at Birmingham, Birmingham, AL, ; [4]Neurosci., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: The Role of PTEN Subcellular Localization in the Regulation of Neuronal Development Nicole Desmet, Annaliese OuYang, Helena Seo, Mackenzi Prina, Meijie Li, Wei Wang, Bryan LuikartMolecular and Systems Biology Geisel School of Medicine at Dartmouth Autism Spectrum Disorder (ASD) is a prevalent neurodevelopmental disorder affecting 1 in 36 children in the United States. While most cases are idiopathic, a growing number have been linked to genetic mutations. Recent genomic sequencing reports indicate that Phosphatase and Tensin Homolog (*PTEN*) is the 6th most commonly mutated gene in patients with ASD. When *PTEN* is mutated, unregulated activation of the AKT/mTOR pathway drives neuronal hypertrophy. While some PTEN mutations result in nuclear enrichment/exclusion of PTEN, how the localization of PTEN regulates its function is unknown.PTEN broadly localizes throughout the cell and subpopulations may have distinct functional impacts. Using PTEN$^{flx/flx}$/Ai14 mice and retroviral-mediated genetic manipulation, endogenous *Pten* can be knocked out and simultaneously reconstituted with *PTEN* fused to localization motifs. By localizing PTEN to the filopodia, post-synaptic density, nucleus, or nuclear-exclusion, we analyzed the importance of subcellular location in regulating neuronal hypertrophy and protrusion formation. In developing hippocampal neurons, *Pten* loss results in increased soma area, and increased spine density, length, and head area. PTEN localized to the filopodia, the post-synaptic density, and nuclear-excluded PTEN all rescue each of the phenotypes observed. These results suggest that PTEN is needed at the membrane to control neuronal growth and spine density. However, nuclear-localized PTEN rescues only the increase seen in dendritic spine head area. This may imply a mechanism through which PTEN-regulated transcription controls spine head area, a crucial characteristic of synapse strength and function. Understanding how PTEN subcellular

localization regulates dendritic growth, filopodial motility, and synaptic physiology will help better understand PTEN loss-associated ASD.

Disclosures: N. Desmet: None. **B.W. Luikart:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.18/A53

Topic: A.07. Developmental Disorders

Support: TEDCO 2023-MCRFD-6182

Title: Ipsc-derived brain organoids to study the mechanisms underlying disease variability in patients with syngap1-intelectual disability (syngap1-id)

Authors: *A. PENN;
Johns Hopkins Univ., Baltimore, MD

Abstract: Rare neurodevelopmental disorders (RNDDs) encompass a spectrum of conditions affecting a minority of the global population yet pose significant challenges due to their heterogeneity and limited understanding. Among these disorders, SYNGAP1 mutations contribute to a range of cognitive impairments, autism spectrum disorder (ASD), and epilepsy. Despite its rarity, SYNGAP1-Intellectual Disability disorder manifests with varying severity, underscoring the need for improved insights into their underlying biological mechanisms. This research project aims to elucidate the molecular pathways driving the heterogeneous disease severity observed in individuals with SYNGAP1 mutations. Employing a multi-faceted approach, we first characterize SYNGAP1-induced pluripotent stem cells (iPSCs) and iPSC-derived brain organoids, comparing them with familial neurotypically-developed (NTD) controls. Subsequently, we identify molecular signatures of intellectual disability (ID) and epilepsy using RNA sequencing, shedding light on the pathological mechanisms underlying these conditions. Finally, we evaluate and establish a SYNGAP1 seizure model, leveraging MaxWell high-density micro-electrode array (HD-MEA) recordings to assess electrical activity and synaptic function in SYNGAP-ID patients with different intensity of seizures. This comprehensive approach aims to enhance our understanding of SYNGAP1-related disorders and pave the way for personalized treatment strategies tailored to individual patients.

Disclosures: A. Penn: None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.19/A54

Topic: A.07. Developmental Disorders

Title: Ion Channels in the SHANK3B Mouse Model of Autism

Authors: *S. GREGORETTI, A. KUNNATHA, J. LARIMORE, G. PHILLIPS, L. JAMES, K. ROACH, R. HARSHMAN, L. GEHNER, N. SMALL, S. B. DUTTON;
Neurosci. and Philosophy, Agnes Scott Col., Atlanta, GA

Abstract: Shank3B mouse models tend to show ASD-like behaviors that are compulsive, repetitive and aggressive, including: self-injurious, repetitive grooming, abnormal social interactions, deficits in recognizing social novelty, anxiety-like behaviors at juvenile age, atypical auditory processing and robust learning impairments (Balaan et.al., 2019, Rendall et.al., 2019). The SHANK family of proteins are responsible for synapse formation and synaptic plasticity at glutamatergic synapses. SHANK3B codes for key PSD proteins that are part of the glutamate receptor protein complex that physically links ionotropic NMDA receptors to metabotropic mGlu5 receptors, a linkage necessary for induction of plasticity. Based on this, our research will explore the behavioral impact of heterozygosity of SHANK3B in a sex dependent manner. We will also use immunohistochemistry to describe the protein expression of ion channels regulated by glutamate and associated with neurodevelopment in the heterozygote. This research will further our understanding of the role of SHANK3B in development.

Disclosures: S. Gregoretti: None. **A. Kunnatha:** None. **J. Larimore:** None. **G. Phillips:** None. **L. James:** None. **K. Roach:** None. **R. Harshman:** None. **L. Gehner:** None. **N. Small:** None. **S.B. Dutton:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.20/A55

Topic: A.07. Developmental Disorders

Title: The Role of Endosomal Trafficking in the SHANK3B Mouse Model of Autism

Authors: *K. ROACH[1], L. GEHNER[1], A. KUNNATHA[1], S. GREGORETTI[1], G. PHILLIPS[1], L. JAMES[1], R. HARSHMAN[1], N. SMALL[1], J. LARIMORE[2], S. B. DUTTON[3];
[2]Neurosci., [3]Biology/ Neurosci. Program, [1]Agnes Scott Col., Atlanta, GA

Abstract: Aberrant connectivity is one molecular mechanism that impacts autism phenotypes, and that altered connectivity is a result of altered dendritic spine volume and density. Postsynaptic densities (PSD) composition is regulated by endosomal trafficking proteins such as AGAP1 and scaffolding proteins, such as the SHANK proteins. SHANK3B is a PSD protein is

part of the glutamate receptor protein complex that physically links ionotropic NMDA receptors to metabotropic mGlu5 receptors, a linkage necessary for induction of plasticity. Using immunohistochemistry we describe how AGAP1-dependent endosomal trafficking protein levels are altered in SHANK3B +/- mice. Understanding how AGAP1-dependent endosomal pathways may contribute to neurodevelopment will further elucidate how proper neuronal connections are formed.

Disclosures: K. Roach: None. **L. Gehner:** None. **A. Kunnatha:** None. **S. Gregoretti:** None. **G. Phillips:** None. **L. James:** None. **R. Harshman:** None. **N. Small:** None. **J. Larimore:** None. **S.B. Dutton:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.21/A56

Topic: A.07. Developmental Disorders

Support: NSF GRFP

Title: Shank3 haploinsufficiency leads to altered gastrointestinal morphology and function in mouse model of Autism Spectrum Disorder

Authors: *G. L. EBERLY[1], M. MANTHEY[2], K. PANG[3], H. HUSSEIN[4], S. KLINGENSMITH[5], P. ANIKEEVA[3];
[1]Hlth. Sci. and Technol., [2]Res. Lab. of Electronics, [3]Brain and Cognitive Sci., [4]Electrical Engin. and Computer Sci., MIT, Cambridge, MA; [5]Biol., Wellesley Col., Wellesley, MA

Abstract: Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders characterized by repetitive behaviors and difficulty with communication. Up to 80% of those with ASD also experience gastrointestinal (GI) symptoms. Despite their prevalence, it is unknown whether GI symptoms are psychosomatic or driven by biological mechanisms. GI functions, including selective absorption and motility, are locally regulated by the enteric nervous system (ENS). In this study, we demonstrate that haploinsufficiency of *SHANK3*, an ASD-linked gene that encodes a glutamatergic synapse scaffolding protein, leads to alterations in GI tract and ENS morphology and function in the Shank3B mouse line. Through histological assays on Shank3B$^{+/+}$, Shank3B$^{+/-}$, and Shank3B$^{-/-}$ mice (n = 5-10, age: 8-12 wks), we demonstrate that Shank3 is expressed in epithelial and endothelial cells, as well as in myenteric neurons, in the small intestine and colon. We find that adult Shank3B$^{-/-}$ and Shank3B$^{+/-}$ mice have significantly altered epithelial and gross morphology, exhibiting smaller villi to crypt length ratio in the proximal small intestine ($^{-/-}$: 7.55 um ± 0.39, $^{+/-}$: 10.18 um ± 0.91, $^{+/+}$: 13.21 um ± 1.18); Shank3B$^{-/-}$ mice also have shorter colon lengths ($^{-/-}$: 6.481 um ± 0.13, $^{+/-}$: 7.39 um ± 0.27, $^{+/+}$: 8.7 um ± 0.62). Morphological changes are accompanied by functional changes in absorption and motility. Shank3B$^{-/-}$ mice have more permeable intestinal walls as indicated by increased

concentration of FITC-Dextran in plasma after oral gavage ($^{-/-}$: 7.32 ug/mL ± 1.00, $^{+/-}$: 4.78 ug/mL ± 0.36, $^{+/+}$: 4.4 ug/mL ± 0.40). Via the carmine dye assay, we also find that whole gastric transit velocity is reduced in Shank3B$^{-/-}$ and Shank3B$^{+/-}$ mice ($^{-/-}$: 0.035 ± 0.0054 mm/min, $^{+/-}$: 0.045 ± 0.0060 mm/min, $^{+/+}$: 0.070 ± 0.008 mm/min). Further *ex vivo* analysis of colonic contractions over 15 minutes reveals that there is no significant difference in number of initiated contractions ($^{-/-}$: 8 ± 0.89, $^{+/-}$: 10.17 ± 1.13, $^{+/+}$: 7.67 ± 0.71), but that individual contraction velocity is reduced in Shank3B$^{-/-}$ mice ($^{-/-}$: 0.67 ± 0.06, $^{+/-}$: 1.16 ± 0.06, $^{+/+}$: 0.99 ± 0.10) and that contraction propagation is disrupted in the distal colon- only 68% ± 5.83 of contractions in Shank3B$^{-/-}$ mice propagated the entire length of the colon, compared to 98% ± 1.67 and 93% ± 4.94 in Shank3B$^{+/+}$ and Shank3B$^{+/-}$ mice, respectively. Histological analysis revealed differences in colon myenteric plexus organization. These results suggest that altered glutamatergic signaling during development may contribute to aberrant adult ENS organization and function and identifies peripheral opportunities for therapeutics focused on relieving GI-comorbidities of ASD.

Disclosures: G.L. Eberly: None. **M. Manthey:** None. **K. Pang:** None. **H. Hussein:** None. **S. Klingensmith:** None. **P. Anikeeva:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.22/A57

Topic: A.07. Developmental Disorders

Support: SFARI #946867

Title: Characterizing and visualizing axon pathology in the uncinate fasciculus in autism spectrum disorder by high-resolution microscopy and machine learning approaches

Authors: S. XIE[1], M. STACKPOLE[1], K. DANG[2], K. KUANG[2], X. LIU[4], A. YAZDANBAKHSH[3], *B. ZIKOPOULOS[2,5];
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Abstract: Autism spectrum disorder (ASD) is a developmental condition marked by deficits in social communication and the presence of restricted and repetitive patterns of behavior. ASD can be approached as a neural communication and connectivity disorder that distinctly affects multiple brain areas, pathways, circuits, and networks. Prefrontal and temporal cortices and the networks they are engaged in are consistently affected in ASD, however, the specific pathology

and mechanisms of disruption in the communication between the two regions remain elusive. To address this gap, we studied the uncinate fasciculus (UF), one of the major long-range pathways that connects medial and orbital prefrontal cortices with temporal regions, using post-mortem human brain tissue and high-resolution light and electron microscopy imaging. Using systematic, unbiased sampling, we measured axon density, diameter, area, myelin thickness, G ratio, and trajectory variabilities in the UF of adults with ASD and sex/age-matched controls. We found significant changes in axon density, myelin thickness, and G ratio of thin, medium, and thick axons in ASD cases. To identify key microscopic axonal configurations distinguishing UF of ASD vs control brains, we a) used thousands of high-resolution microscopy images of the UF for supervised training and optimization of machine learning algorithms and convolutional neural networks (CNNs) to classify ASD vs neurotypical microscopy sections with high accuracy, and b) used the highest performing CNN to generate saliency maps highlighting distinct ASD- and control-UF patterns in histopathology sections from microscopy. These patterns can provide insights about core features of a major long-range white matter pathway and distinct patterns of structural features of axons that underlie ASD pathophysiology. This approach can be generalized for systematic study of pathways in the human brain and offer a set of metrics for the study of heterogeneity in neurotypical adults and in disorders like ASD.

Disclosures: S. Xie: None. **M. Stackpole:** None. **K. Dang:** None. **K. Kuang:** None. **X. Liu:** None. **A. Yazdanbakhsh:** None. **B. Zikopoulos:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.23/A58

Topic: A.07. Developmental Disorders

Support: Simons Foundation SFARI Grant 946867
NIH NIMH Grant R01MH118500

Title: Machine learning approaches to study and visualize axon pathology in short- and long-range pathways of the cortical white matter in autism

Authors: *A. YAZDANBAKHSH, K. DANG, K. KUANG, X. LIU, S. XIE, S. ALSHANNIEK, B. ZIKOPOULOS;
Boston Univ., Boston, MA

Abstract: Axon pathology is at the core of disruptions in cortical connectivity in autism spectrum disorder (ASD). However, the extent and distribution of disruption in a) short- and long-range cortical pathways and b) pathways linking association cortices or other cortices and subcortical structures are unknown. Neuroanatomical analysis of high-resolution features of individual axons, such as density, trajectory, branching patterns, and myelin in multiple cortical pathways, are labor-intensive and time-consuming. This limits large-scale studies that otherwise

can help identify core pathways that are altered in ASD and likely mechanisms that underly neural communication disruption. To automate and optimize analysis and visualization of patterns of disruption, we customized state-of-the-art ensembles of machine learning techniques to quantify the requisite power of multiscale optical and electron microscopy for accurately classifying neurotypical and ASD postmortem brain histopathology sections. We used fixed postmortem cortical tissue samples containing white matter below prefrontal cortices (PFC), including medial cingulate areas 32, 25, and 24, lateral PFC areas 46, 9, and 10, and orbital PFC areas 13, 11, for an extensive survey of axon pathology in ASD. We trained and optimized machine learning algorithms and used convolutional neural network (CNN) approaches to classify white matter cortical pathways. We measured the generalizability of the detected axon patterns for ASD and neurotypical brains in a given brain area across a) cases, b) areas, and c) postmortem interval.Moreover, we visualized key structural patterns contributing to correct CNN classification using gradient and occlusion methods to obtain saliency maps. Our results provide key features of typical cortical white matter pathways and specific patterns of axon status in ASD, whether it is within superficial or deep white matter, which include short- and long-range pathways, respectively. Moreover, we can detect generalized patterns of pathology irrespective of white matter depth. These include, but not limited to, trajectory variability, axon density, and size differences, visualized in saliency maps. The data will be used to model common or divergent modes of communication in multiple short- and long-range association cortical and subcortical pathways in ASD, with important implications for the development of targeted therapeutic interventions.

Disclosures: A. Yazdanbakhsh: None. **K. Dang:** None. **K. Kuang:** None. **X. Liu:** None. **S. Xie:** None. **S. Alshanniek:** None. **B. Zikopoulos:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.24/A59

Topic: A.07. Developmental Disorders

Support: NIGMS grant 5T34GM140958
NIMH grant 1R01MH132921
Boettcher Foundation

Title: Haploinsufficiency of the autism-associated δ-catenin mutation is sufficient to induce social dysfunction in mice

Authors: *E. HINCHLIFFE[1], V. ARAGON[1], S. ROH[1], R. ROACH[2], R. LEE[3], S. KIM[3]; [1]Colorado State Univ., Fort Collins, CO; [2]Col. of Vet. Med. and Biomed. Sci., Colorado State Univ., Fort Collins, CO; [3]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Social behavior is essential to survive for many species, and various mental disorders have social impairment as a primary symptom. Research suggests that synaptic activity and signaling can regulate social behavior. However, the links between synaptic regulation and social behavior are not completely understood. δ-catenin functions as an anchor for the glutamatergic AMPA receptor (AMPARs) to regulate synaptic activity in excitatory synapses. Mutations in the δ-catenin gene are found in autism patients from multiple families and induce a loss of δ-catenin functions at excitatory synapses, which is thought to be the etiology of autism in people. In fact, patients heterozygous for deletions or loss-of-function variants of the δ-catenin gene exhibit a variety of features of autism. Therefore, δ-catenin heterozygous mutant is a valuable loss-of-function model to investigate ASD pathophysiology caused by δ-catenin haploinsufficiency. Here, we used mice harboring one copy of human autism-associated δ-catenin missense mutations, a glycine 34 to serine (G34S), to address whether δ-catenin haploinsufficiency that mimics the human condition is sufficient to induce social dysfunction in animals. To test this, the reciprocal social interaction test to examine social interaction between two freely moving mice was performed. We found that the total number of contacts and total duration of contacts were significantly reduced in both female and male G34S heterozygous (HET) mice. Furthermore, synaptic δ-catenin and AMPAR subunits (GluA1 and GluA2) levels were significantly reduced in the cortex of HET mice. However, the open field test showed normal locomotor activity and anxiety levels in these mice. Therefore, we discover that δcatenin haploinsufficiency is sufficient to induce social dysfunction in mice.

Disclosures: E. Hinchliffe: None. **V. Aragon:** None. **S. Roh:** None. **R. Roach:** None. **R. Lee:** None. **S. Kim:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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Topic: A.07. Developmental Disorders

Support: NIMH grant 1R01MH132921
Jerome Lejeune Foundation
NIH/NCATS Colorado CTSA Grant UL1 TR002535
Boettcher Foundation
Colorado State University
NIMH Grant R01MH126017

Title: The autism-associated loss of δ-catenin functions disrupts social behavior

Authors: *R. ROACH[1], H. MENDEZ-VAZQUEZ[1], K. NIP[1], S. CHANDA[1], M. SATHLER[1], M. MOSELEY[1], R. LEE[1], J. ARIKKATH[2], S. KIM[1];
[1]Colorado State Univ., Fort Collins, CO; [2]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: δ-catenin is expressed in excitatory synapses and functions as an anchor for the glutamatergic AMPA receptor (AMPAR) GluA2 subunit in the postsynaptic density. The glycine 34 to serine (G34S) mutation in the δ-catenin gene has been found in autism spectrum disorder (ASD) patients and results in loss of δ-catenin functions at excitatory synapses, which is presumed to underlie ASD pathogenesis in humans. However, how the G34S mutation causes loss of δ-catenin functions to induce ASD remains unclear. Here, using neuroblastoma cells, we identify that the G34S mutation increases glycogen synthase kinase 3β (GSK3β)-dependent δ-catenin degradation to reduce δ-catenin levels, which likely contributes to the loss of δ-catenin functions. Synaptic δ-catenin and GluA2 levels in the cortex are significantly decreased in mice harboring the δ-catenin G34S mutation. The G34S mutation increases glutamatergic activity in cortical excitatory neurons while it is decreased in inhibitory interneurons, indicating changes in cellular excitation and inhibition. δ-catenin G34S mutant mice also exhibit social dysfunction, a common feature of ASD. Most importantly, pharmacological inhibition of GSK3β activity reverses the G34S-induced loss of δ-catenin function effects in cells and mice. Finally, using δ-catenin knockout mice, we confirm that δ-catenin is required for GSK3β inhibition-induced restoration of normal social behavior in δ-catenin G34S mutant animals. Taken together, we reveal that the loss of δ-catenin functions arising from the ASD-associated G34S mutation induces social dysfunction via alterations in glutamatergic activity and that GSK3β inhibition can reverse δ-catenin G34S-induced synaptic and behavioral deficits.

Disclosures: R. Roach: None. **H. Mendez-Vazquez:** None. **K. Nip:** None. **S. Chanda:** None. **M. Sathler:** None. **M. Moseley:** None. **R. Lee:** None. **J. Arikkath:** None. **S. Kim:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.26/A61

Topic: A.07. Developmental Disorders

Support: Colorado State University
Jerome Legeune Foundation
NIH grant (1R01MH132921)

Title: Prenatal exposure to valproic acid reduces synaptic δ-catenin levels and disrupts ultrasonic vocalization in neonates

Authors: *S. ROH, H. MENDEZ-VAZQUEZ, M. SATHLER, M. DOOLITTLE, A. ZAYTSEVA, S. KIM;
Colorado State Univ., Fort Collins, CO

Abstract: Valproic acid (VPA) is an effective and commonly prescribed drug for epilepsy and bipolar disorder. However, children born from mothers treated with VPA during pregnancy exhibit an increased incidence of autism spectrum disorder (ASD). Although VPA may impair

brain development at the cellular level, the mechanism of VPA-induced ASD has not been completely addressed. A previous study has found that VPA treatment strongly reduces δ-catenin mRNA levels in cultured human neurons. δ-catenin is important for the control of glutamatergic synapses and is strongly associated with ASD. VPA inhibits dendritic morphogenesis in developing neurons, an effect that is also found in neurons lacking δ-catenin expression. We thus hypothesize that prenatal exposure to VPA significantly reduces δ-catenin levels in the brain, which impairs glutamatergic synapses to cause ASD. Here, we found that prenatal exposure to VPA markedly reduced δ-catenin levels in the brain of mouse pups. VPA treatment also impaired dendritic branching in developing mouse cortical neurons, which was partially reversed by elevating δ-catenin expression. Prenatal VPA exposure significantly reduced synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor levels and postsynaptic density 95 (PSD95) in the brain of mouse pups, indicating dysfunctions in glutamatergic synaptic transmission. VPA exposure also significantly altered ultrasonic vocalization (USV) in newly born pups when they were isolated from their nest. Moreover, VPA-exposed pups show impaired hypothalamic response to isolation, which is required to produce animals' USVs following isolation from the nest. Therefore, these results suggest that VPA-induced ASD pathology can be mediated by the loss of δ-catenin functions.

Disclosures: S. Roh: None. **H. Mendez-Vazquez:** None. **M. Sathler:** None. **M. Doolittle:** None. **A. Zaytseva:** None. **S. Kim:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.27/A62

Topic: A.07. Developmental Disorders

Support: 112-2320-B-002 -035 -MY3

Title: Odor-induced c-fos expression in Dlgap2 mutant mice, a mouse model of autism spectrum disorder

Authors: *L.-J. LEE[1], Y.-F. CHEN[2], K.-Y. LEE[2];
[1]Anat. and Cell Biol., Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan; [2]Chang Gung Mem. Hosp., keelung, Taiwan

Abstract: Smell problems are correlated with autism spectrum disorder (ASD). A microdeletion at the 8p23 terminal region had been identified in a Taiwanese boy with ASD, and the DLGAP2 gene had been speculated as a candidate for ASD. In this study, we characterized the olfactory phenotypes in Dlgap2 mutant mice. Dlgap2 Homo mice seemed not interested in food odors such as bananas, and almonds but exhibited greater activities when encountering bedding of other unfamiliar cages. We then checked the expression of c-fos as the index of odor-induced neuronal activation. Exposure to banana extract induced c-fos expression in the olfactory bulb, anterior

olfactory nuclei, piriform cortex, and bed nucleus in WT mice but not in Dlgap2 Homo. Exposure to bedding odor elicited c-fos expression in the olfactory bulb, medial prefrontal cortex, and olfactory tubercle in both genotypes; piriform cortex, endopiriform nuclei, bed nucleus, lateral olfactory tract, cortical amygdaloid nucleus, medial amygdala, lateral entorhinal cortex, and ventromedial hypothalamus in WT mice; medial preoptic area in Dlgap2 Homo. Our study not only advanced our knowledge of the olfactory system but also comprehended the pathogenesis of neurodevelopmental disorders such as ASD, which may further improve the diagnosis and treatments.

Disclosures: L. Lee: None. **Y. Chen:** None. **K. Lee:** None.

Poster

PSTR435: Cellular, Synaptic, and Molecular Defects in Autism

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR435.28/A63

Topic: A.07. Developmental Disorders

Support: Weill Neurohub Novel Therapies for Neurodevelopmental Disorders
Simons Foundation SFARI Investigator
NSF GRFP

Title: Rescue of degraded tactile coding in the Scn2a+/- mouse model of ASD

Authors: *K. VANDEMARK[1], H. R. MONDAY[1], L. RODRIGUEZ[1], D. FELDMAN[2,3]; [1]Dept. of Neurosci., UC Berkeley, Berkeley, CA; [2]Mol. & Cell Biol. Dept., UC Berkeley, Berkeley, CA; [3]Department of Neuroscience, UC Berkeley, Berkeley, CA

Abstract: Of known high-risk ASD genes in humans, the *Scn2a* gene is one of the most strongly linked to ASD through *de novo* heterozygous loss-of-function mutations (Satterstrom et al., 2020). We model this using *Scn2a* heterozygous (+/-) mice. Despite its strong association with ASD, little is known about how *Scn2a* loss-of-function mutations lead to impaired sensory processing, and what therapeutic strategies might rescue sensory function.
We studied how *Scn2a* heterozygosity impacts neural coding in mouse primary whisker somatosensory cortex (wS1) using *in vivo* extracellular single-unit recordings in awake, task-engaged mice. In L2/3 RS units (presumed pyramidal cells), there was no significant difference in spontaneous or whisker-evoked firing rates between *Scn2a*Het and wildtype (WT) mice. L2/3 FS units (presumed PV cells) showed significantly reduced whisker-evoked firing rates, indicating PV hypofunction in *Scn2a*Hets. Strikingly, *Scn2a*Het mice showed a pronounced degradation of whisker somatotopic tuning and map organization in L2/3 and L4, including substantial broadening of whisker tuning for single RS units and local field potentials (LFP). We also see near-complete loss of map-level somatotopy measured with intrinsic signal optical imaging (ISOI).
Transcriptional activation offers a potential strategy for restoring neural circuit function in some

single-gene neurological disorders (Sanders et al, 2018). We used CRISPRa to elevate expression of the *Scn2a* gene and then asked whether this rescues degraded tactile coding in adult *Scn2a*Het mice. We systemically delivered CRISPRa via retro-orbital injection of blood-brain-penetrant AAVs at P30-40, and then recorded extracellularly in anesthetized mice to characterize single-whisker tuning in L2/3 and L4 RS units at P75-90. Results showed, on average, sharp single-whisker tuning in L2/3 and L4 RS units in CRISPRa-injected *Scn2a*Hets, compared to broadly tuned *Scn2a*Het controls. We also find that L2/3 and L4 FS units show WT-level whisker-evoked firing rates in CRISPRa-injected *Scn2a*Het mice. Lastly, somatotopic map precision measured using ISOI is restored in >80% of CRISPRa-injected *Scn2a*Het mice. However, in WT mice, we find that CRISPRa injection significantly reduces L2/3 and L4 FS unit whisker-evoked firing rates compared to WT controls. Overall, we find that systemic CRISPRa delivery in adult *Scn2a*Het mice rescues degraded tactile codes, and restores somatotopic map precision. Future experiments will determine whether cortical circuits in wS1 are the site of rescue.

Disclosures: K. Vandemark: None. **H.R. Monday:** None. **L. Rodriguez:** None. **D. Feldman:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: /

Topic: A.08. Development of Neural Systems

Support: NIH/NCI 5K22CA258953

Title: When good things go off TRK: the intersection of neuroscience & oncology

Authors: *S. PATTWELL;
Seattle Children's Res. Inst., Seattle, WA

Abstract: Embryogenesis, and neurodevelopment in particular, comprise an elegant and well-orchestrated series of tightly regulated events, culminating in an organized and highly functioning organism. Cancer, on the other hand, can often be viewed as an uncontrolled, unrestrained, genetically chaotic disease, lacking the precise spatial and temporal rigidity associated with normal development. While appearing to be on opposite sides of the organizational spectrum, the similarities between early neurodevelopment and oncogenesis are numerous and understanding the complexities of one may help to inform perplexing intricacies of the other. The link between neurodevelopmental signaling and cancer initiation, maintenance, and metastasis has long been known for several members of the Wnt, Hedgehog, and Notch pathways and years of gene-level analyses have provided a wealth of knowledge and mechanistic insight. As advances in next generation sequencing allow for deeper characterization of genetic programs, it is increasingly possible to explore various isoforms of cancer associated genes.

Temporally-regulated alternative splicing choices are vital for proper development yet the wrong splice choice can be detrimental, such as in the context of cancer. It is widely known that neurotrophins and their receptors (TrkA, TrkB, and TrkC) are instrumental in laying the foundation of the developing nervous system and that they remain critical for proper neuronal functioning throughout life. Our work highlights a previously unidentified role for an alternatively spliced neurotrophin receptor in neurodevelopment, embryogenesis, transformation, and oncogenesis across multiple tumor types in humans and mice. This specific isoform, TrkB.T1, is the predominant *NTRK2* isoform across embryonic organogenesis, and forced overexpression of this embryonic pattern causes multiple solid and nonsolid tumors in mice in the context of tumor suppressor loss. TrkB.T1 also emerges as the predominant *NTRK* isoform expressed in a wide range of adult and pediatric tumors, including those harboring various NTRK fusions. Affinity purification-mass spectrometry proteomic analysis reveals distinct interactors with known developmental and oncogenic signaling pathways such as Wnt, transforming growth factor-β, Sonic Hedgehog, and Ras and preliminary data reveals interactions with immune cells within the tumor microenvironment. This work hopes to address the fundamental question of how neurodevelopmental processes can go awry in cancer, while seeking to better characterize the role of TRKs, in normal developmental processes and oncogenesis.

Disclosures: S. Pattwell: None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.01/A64

Topic: A.08. Development of Neural Systems

Title: Making predictions about neural patterning using a 4D transcriptional model of the Caenorhabditiselegans embryo

Authors: *K. BOONE[1], B. YARBROUGH[2], M. CHAW[4], M. NGUYEN[1], M. KITTISOPIKUL[1], B. J. ARTHUR[3], J. BUI[5], G. IHRKE[1], R. CHRISTENSEN[1], H. SHROFF[1]; [1]Janelia Res. Campus, Ashburn, VA; [2]Project Pipeline Support, [3]Howard Hughes Med. Inst., Ashburn, VA; [4]Dept. of Genome Sciences, Univ. of Washington, Seattle, WA; [5]Howard Hughes Med. Inst. - Janelia Res. Campus, Ashburn, VA

Abstract: During embryogenesis, rapid tissue rearrangement takes place, moving cells toward positions critical for final architecture and function. How these rearrangements interact with other molecular and cellular events driving morphogenesis is not well understood. To interrogate these interactions, we are combining 4D tracking of nuclear positions with pre-existing single cell-RNAseq data[1] to generate a 4D transcriptional model of the *Caenorhabditis elegans* embryo. *C. elegans* embryos offer an optically transparent and genetically tractable model with only 558 cells and a short generation time. We focus on elongation, a late stage when the embryo

lengthens along its longitudinal axis. While hypodermal cells and body wall muscles are the primary drivers of this event[2], we show an unanticipated role for elongation in shaping neuronal structure. The *C. elegans* nervous system is simple with only 222 neurons in the embryo, most of which innervate a ring-shaped neuropil that functions as the brain[3]. Live imaging of developing embryos labeled with pan-neuronal GFP, using diSPIM (dual-view inverted Selective Plane Illumination Microscopy) imaging, demonstrated that early nerve ring morphology has a 'horseshoe' shape with many bilateral neuron pairs contacting dorsally but not ventrally, leaving the ventral midline open. Time-course imaging revealed a critical period during which neurons make contact along the ventral midline to create the 'closed' ring-like neuropil. We hypothesized that closure was dependent on embryo elongation and found that mutations in the genes *emb-9* and *pat-3*, which disrupt elongation, prevents closure of the nerve ring. We further confirm loss of specific cell-cell contacts at the ventral midline by imaging the GFP-labeled AIY neuron pair. Published electron and fluorescence microscopy data in larval and adult animals show bilateral cell-cell contacts along the ventral midline between AIY neurites. Contacts form normally in wild-type embryos while elongation-defective *pat-3* mutant embryos lose these contacts. We suspect ventral closure plays a critical role in synaptic patterning and cell adhesion. To test this hypothesis, we are combining our 4D transcriptional models with transgenic approaches to observe synaptic patterning in wild type and elongation-defective embryos and identify candidate adhesion genes expressed in ventrally contacting neurons during the critical period of nerve ring closure.

Disclosures: K. Boone: None. **B. Yarbrough:** None. **M. Chaw:** None. **M. Nguyen:** None. **M. Kittisopikul:** None. **B.J. arthur:** None. **J. Bui:** None. **G. Ihrke:** None. **R. Christensen:** None. **H. Shroff:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.02/A65

Topic: A.08. Development of Neural Systems

Support: NIH Grant R01Es033056-03

Title: The effects of maternal high-fat diet on offspring microglial development and metabolomes

Authors: *S. KUMAR, S. BILBO;
Duke Univ., Durham, NC

Abstract: More than 50% of women in the United States are diagnostically overweight or obese when they become pregnant. Furthermore, elevated maternal weight is associated with multiple adverse outcomes for offspring, including increased incidence of mental health disorders such as depression, and social and communication disorders. However, the mechanisms by which dietary

intake during pregnancy imparts long-term offspring neural dysfunction remain poorly understood. Using a maternal high-fat diet model, our lab has demonstrated that male offspring microglia display increased phagocytosis of serotonin neurons in the dorsal raphe nucleus at E14.5 which leads to a decrease in brain serotonin levels that persists throughout adulthood. To understand the mechanisms behind this increased engulfment we have performed live imaging of microglia-serotonin neuron interactions in embryonic brain slices. In parallel, we will investigate how maternal diet influences offspring microglial metabolomes by performing untargeted lipidomics and metabolomics on isolated E14.5 microglia. Taken together, our work will lead to an improved understanding of the consequences of high-fat diet on microglial development and function.

Disclosures: S. Kumar: None. **S. Bilbo:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.03/A66

Topic: A.08. Development of Neural Systems

Title: The Effects of Fetal Alcohol Exposure on Impulsive Choice in Rats

Authors: *I. YATES[1], S. K. SALAND[2], M. KABBAJ[3];
[1]Florida State Univ., Tallahassee, FL; [2]Dept. of Biomed. Sci. & Program in Neurosci., Florida State Univ. Program In Neurosci., Tallahassee, FL; [3]Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Title: The effects of fetal alcohol exposure on impulsive choice in rats**Authors:** Ian Yates, Samantha K. Saland, and Mohamed KabbajWhile clinical data has shown that fetal alcohol exposure is correlated with alterations in performance on tasks measuring impulsivity, studies have not yet investigated the mechanisms underlying these changes. Additionally, outside of the context of fetal alcohol exposure, previous research has indicated that delay discounting, a model of impulsive choice, may be predictive of susceptibility to develop a substance use disorder in humans and rodents. Since individuals who are exposed to alcohol during fetal development show alterations in both levels of impulsivity and risk of developing a substance use disorder, investigating the mechanisms underlying changes in levels of impulsivity and how these are associated with the risk to developing a substance use disorder is crucial for a comprehensive understanding of these outcomes. To examine the effects of fetal alcohol exposure on impulsive choice in adulthood using a delay discounting task in both male and female rats, adult female rats were given access to either 5% ethanol or water for 4h/day for a total of 2 weeks prior to pregnancy. Following pregnancy, access to 5% ethanol or water was maintained for the entirety of gestation until birth. Once the offspring aged to adulthood (8wks), impulsive choice in a delay discounting task was assessed in both males and females using an adjusting delay procedure until performance stabilized. In the establishment of our current

drinking protocol, results showed that blood alcohol concentrations were consistent with recent publications utilizing a similar approach, demonstrating the validity of our drinking paradigm as a model of moderate alcohol exposure. Additionally, there were individual differences in the performance of the adjusting delay discounting task in water-exposed controls. Overall, we observed blood alcohol concentrations within the moderate exposure range using our alcohol exposure protocol, alongside performance differences in the delay discounting task among individual controls. Given that individual differences are a prominent feature of substance use disorders, it is crucial to better understand these variations to develop more effective therapeutic approaches. Our ongoing work is focused on examining the effect of fetal alcohol exposure on performance in a delay discounting task.

Disclosures: I. Yates: None. **S.K. Saland:** None. **M. Kabbaj:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.04/A67

Topic: A.08. Development of Neural Systems

Support: SNSF Grant

Title: Maternal microbiota to fetus: exploring the role of gut-derived short chain fatty acids in offspring autonomic circuits and physiology

Authors: *N. ELSHAREIF[1], C. K. GAVINI[2], V. MANSUY AUBERT[2];
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Abstract: The rising prevalence of obesity and type II diabetes early in life necessitates innovative approaches to address metabolic dysfunction. Western dietary habits, characterized by high saturated fat, sugar, and low fiber, disrupt the gut microbiome and likely exacerbating metabolic imbalances. These imbalances are further compounded by dysfunction of the autonomic nervous system, leading to altered gut motility, nutrient sensing, and an increase in insulin resistance as modified sympathetic and parasympathetic signaling play critical roles in metabolic homeostasis.[1]One significant effect of the gut microbiota is the fermentation of dietary fiber, which produces short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. Increasing fiber intake and SCFA production has been found to have beneficial metabolic effects on fasting glucose levels, satiety, and mood through modulation of the gut-brain axis. [2,3]Recent research has highlighted the pivotal role of maternal gut microbiota in offspring metabolic resilience where microbiota and maternal propionate production influenced body weight, glucose levels, and heart function presumably via neural regulation.[4] We proposed to better define the cellular and molecular mechanism underlying the effect of maternal propionate on offspring neural circuitry that regulates glucose homeostasis and energy balance. To this end we manipulated maternal gut microbiota using diets, or antibiotics and we evaluated expression

profiles of propionate downstream signaling proteins and downstream targets in sympathetic ganglia. We also evaluated the consequence of knocking out SCFA receptors on offspring autonomic neural circuit and physiology. These efforts aim to understand the molecular mechanisms linking the parental gut microbiota to offspring autonomic function in obesity and type II diabetes.

1. Cook, T. M. & Mansuy-Aubert, V. Communication between the gut microbiota and peripheral nervous system in health and chronic disease. *Gut Microbes* **14**, 2068365 (2022). https://doi.org/10.1080/19490976.2022.2068365
2. Blaak, E. E. *et al.* Short chain fatty acids in human gut and metabolic health. *Benef Microbes* **11**, 411-455 (2020). https://doi.org/10.3920/BM2020.0057
3.Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol* **16**, 461-478 (2019). https://doi.org/10.1038/s41575-019-0157-3
4. Kimura, I. *et al.* Maternal gut microbiota in pregnancy influences offspring metabolic phenotype in mice. *Science* **367** (2020). https://doi.org/10.1126/science.aaw8429

Disclosures: N. Elshareif: None. **C.K. Gavini:** None. **V. Mansuy Aubert:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.05/A68

Topic: A.08. Development of Neural Systems

Support: NSF
TGI

Title: The Dark Side of Light: Geospatial Analysis and Anatomical Investigation of the Effects ofLight Pollution on the Maternal Paraventricular Nucleus During Pregnancy

Authors: I. SMITH[1], *C. MARTIN-FAIREY[2];
[1]Life Sci., Harris-Stowe State Univ., St. Louis, MO; [2]Harris-Stowe State Univ., Saint Louis, MO

Abstract: Exposure to light pollution during pregnancy has been associated with poor gestational, maternal, and fetal health outcomes in mammals. The hypothalamic paraventricular nucleus (PVN) plays a critical role in regulating neuroendocrine changes during pregnancy in rodents. Melatonin, a hormone involved in circadian rhythm regulation, is produced by the pineal gland in response to darkness and has been shown to play an important role in fetal development and maternal health during pregnancy. In this study, we used Geographic Information System (GIS) analyses to identify areas with high levels of light pollution and map them against data on adverse pregnancy outcomes, such as low birth weight and preterm birth. We found that there is a clear relationship between exposure to light pollution and poor pregnancy outcomes. We then investigated the effects of a light pulse during rodent pregnancy on clock gene expression and c-

fos activation in the PVN. Previous findings suggest that exposure to a light pulse during pregnancy can affect clock gene expression in the PVN of rodents, potentially through alterations in melatonin production. These results will provide important insights into the potential effects of light pollution on maternal and fetal health outcomes, highlighting the need for further research in this area. Moreover, the study further supports the critical role of the PVN in the regulation of pregnancy-related neuroendocrine changes, and the influence of melatonin production on the PVN function during pregnancy. Understanding the molecular mechanisms underlying these effects may have important implications for mammalian maternal and fetal health.

Disclosures: I. Smith: None. **C. Martin-Fairey:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

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Program #/Poster #: PSTR436.06/A69

Topic: A.08. Development of Neural Systems

Support: the Région Normandie through the NanoCellConnection-Chaire d'Excellence programme

Title: Dynamic behavior of subarachnoid trabeculae in early postnatal mice revealed by time-lapse observation of super-resolution microscopy

Authors: *H. KOMURO[1,2,4], A. DEBONNE[1,2,4], M. BÉNARD[1,2,4], C. CHAMOT[1,2,4], A. LEBON[1,2,4], D. SCHAPMAN[1,3,5], A. ARABO[1], L. GALAS[1,2,4];
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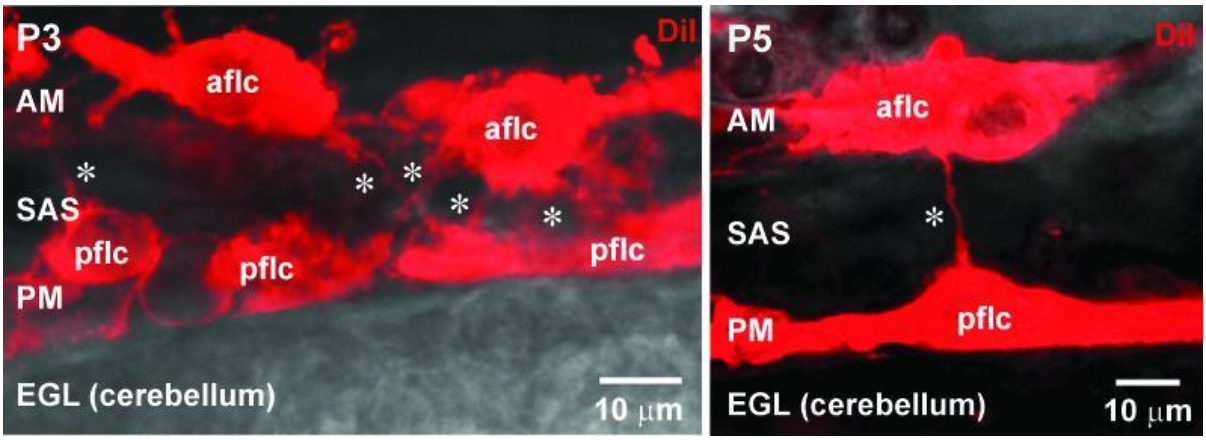
Abstract: Mammalian brains are covered by the meninges, consisting of dura mater, arachnoid mater (AM), and pia mater (PM), and bathed in cerebrospinal fluid (CSF) in the subarachnoid space (SAS) between the AM and the PM. In the SAS, subarachnoid trabeculae (SATs) anchor brains to the AM and stabilize positions during head movement. Although new roles for SATs have been proposed in control of CSF flow, recovery after hemorrhage, and post-traumatic chronic subdural hematomas, the difficulties of visualizing SATs in vivo and in vitro keep the role of SATs poorly understood. To overcome this problem, in this study, we examined SAT behavior in live tissues using super-resolution microscopy and fluorescent dyes. Brains with meninges or leptomeninges were dissected from early postnatal (P1-P10) CD-1 mice (both sexes), and sagittally sectioned at 200-300 μm -thickness using a vibratome. Slices were stained with 5 μg/ml of DiI, DIO, and/or DiA, and placed in a micro-incubation chamber (37^{o}C, 5% CO_2) attached to the stage of a super-resolution microscope (Leica, STELLARIS 8). The use of an x93 glycerol immersion objective (N.A. 1.30) and an additional digital zoom factor (x0.75-x3.0) allowed the visualization of SATs in the SAS. Time-lapse images of SATs were taken every 1-5 seconds for up to 2 hours. As presented in photos, SATs (marked by asterisks) were

observed in the SAS located above the dorsal surface of the cerebellar external granular layer (EGL) of P3 and P5 mice. In some cases, arachnoidal fibroblast-like cells (aflc) and pial fibroblast-like cells (pflc) were connected by a single SAT-like process. The size of SATs varied considerably, ranging between 200-1000 nm. At this developmental stage, SATs were not immovable structures, but exhibited alterations in morphology (such as extension, retraction, and branching) and connections in the SAS within a short period of time. These results demonstrate dynamic processes of SAT formation in developing animals, providing insights for regeneration of SATs in the SAS after traumatic brain injury and after microsurgical techniques in brains.



Disclosures: H. Komuro: None. **A. Debonne:** None. **M. Bénard:** None. **C. Chamot:** None. **A. Lebon:** None. **D. Schapman:** None. **A. Arabo:** None. **L. Galas:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.07/A70

Topic: A.08. Development of Neural Systems

Title: Ultra-high-resolution neuroimaging of the postmortem human brain at 3T

Authors: *Q. SMITH[1], T. R. KOSCIK[2];
[1]Arkansas Children's Res. Inst., Little Rock, AR; [2]Pediatric Neurol., Arkansas Children's Res. Institute/University of Arkansas for Med. Sci., Little Rock, AR

Abstract: Cortical laminar architecture is the result of microscale neuronal components (e.g., neurites, neurons, and glia, etc.) segregating into mesoscale laminar structures across the macroscale of the cerebral cortex. While laminar organization is critical for cognitive function, it is too small to be studied with conventional MRI and too widespread for practical histological methods. To address this gap, we have developed procedures to gather ultra-high-resolution MR images using common 3T scanners that have sufficient resolution to quantify individual cortical laminar architecture across the entire cerebral cortex. We have established a novel collaboration

with state-run organ and tissue donation services, the Arkansas Regional Organ Recovery Agency, providing access to more than 500 neurotypical whole brain specimens annually. To date we have acquired and prepared 20 brain specimens from individuals aged 2 months to 80+ years. Whole-Brain Preservation: Whole-brain specimens are fixed by immersion in formaldehyde-based fixative for a minimum of 12 weeks to ensure thorough and even fixation. Each specimen is suspended in fixative using a hairnet to reduce distortion of soft brain tissue. Specimen Preparation for MRI: Following fixation, each specimen is enclosed in a customized scanning vessel, and degassed twice for 24 hours over the course of two weeks to remove trapped air bubbles that create MRI artifacts. MRI Acquisition: MR acquisitions were completed on a Siemens Prisma 3T scanner overnight or weekends. To acquire images with adequate signal-to-noise, we capitalize on the unlimited scan duration afforded by ex vivo specimens. For each brain specimen, we acquire 3 anisotropic images with in-plane resolution of ~150 microns and slice thickness of 400 microns. Images are then resampled to 150 micron isotropic and combined. Ultra-high-resolution Image Processing: Images are denoised and corrected for intensity inhomogeneity, having adapted techniques designed for conventional resolution images for application at a ~200x finer resolution. Our results demonstrate that the cortical laminar are resolvable using a 3T scanner and postmortem specimens. Moreover, our approach demonstrates a set of techniqu es than can be applied in a high-throughput manner to generate population-level estimates of homology and variation in cortical laminar architecture.

Disclosures: Q. Smith: None. **T.R. Koscik:** None.

Poster

PSTR436: Development of Neural Systems

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.08/A71

Topic: A.08. Development of Neural Systems

Support: Canada First Research Excellence Fund
Canadian Institutes of Health Research
Children's Health Foundation
New Frontiers in Research Fund
Brain Canada
Molly Towell Perinatal Research Foundation

Title: Antenatal maternal stress, fetal brain development, and infant cognitive outcomes explored using neuromelanin MRI

Authors: S. AL-SAOUD[1], *E. S. NICHOLS[2], D. SEGUIN[3], E. G. DUERDEN[4];
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Abstract: Antenatal maternal stress is associated with adverse cognitive outcomes in infants, and may be mediated by alterations in the hippocampus and dopaminergic projections from the midbrain's ventral-tegmental area (VTA), which are foundational for memory processes. Recent advancements in neuromelanin magnetic resonance imaging (NM-MRI), has offered a unique and non-invasive way to examine dopamine concentrations in the human midbrain, reflected in NM signal changes in the ventral tegmental area (VTA) and substantia nigra (SN).
The present study aimed to 1) examine the association between prenatal maternal stress and fetal hippocampal volumes; 2) examine the association between fetal hippocampal volumes and VTA-SN neuromelanin signal change in infants; and 3) examine the association between VTA-SN neuromelanin signal change and cognitive outcomes in infants.
Maternal stress was assessed twice in utero, separated by a duration of 2-4 weeks, and once post-birth in 11 pregnant women (22-41 years old) using the Perceived Stress Scale (PSS), a 10-item questionnaire that has been validated for use in pregnant women. Hippocampal volumes were measured in 11 fetuses at timepoint 1 (28.6-36.4 weeks' gestation) and timepoint 2 (31-38 weeks' gestation) using a T1-weighted 3T MRI image.
11 infants (5-17 weeks of age) were scanned with a modified NM-MRI protocol using a three-dimensional gradient recalled echo sequence with magnetization transfer (MT) contrast (~5 minutes) on a 3T Prisma fit MRI scanner (Siemens, Erlangen, Germany). Cognitive outcomes were assessed using the Ages and Stages Questionnaire – Third Edition (ASQ-3).
Maternal stress at timepoint 2 significantly predicted fetal hippocampal volumes at timepoint 2 ($p<.001$). Further, fetal hippocampal volumes at timepoint 2 predicted of VTA/SN NM-MRI signal change ($p<0.05$) in infants. Lastly, VTA/SN NM-MRI signal change predicted of problem-solving scores among infants ($p<.005$).
Findings indicate that stress during the third trimester of pregnancy can have lasting effects on the developing brain, and memory-related functions in infants. NM-MRI has the potential to enhance our understanding of underlying pathophysiological mechanisms that influence cognitive outcomes among infants.

Disclosures: S. Al-Saoud: None. **E.S. Nichols:** None. **D. Seguin:** None. **E.G. Duerden:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.09/A72

Topic: A.08. Development of Neural Systems

Title: The medial pulvinar supports the functional development of thalamocortical circuits subserving working memory in primates

Authors: *J. T. SCOTT, G. GU, A. Y. FAN, J. A. BOURNE;
Natl. Inst. of Mental Hlth., NIH, Bethesda, MD

Abstract: The interplay of the thalamus and cortex during early postnatal life is crucial for cultivating cortical function in adulthood. In primates, including humans, adult cognition is supported by the medial pulvinar (PM), a higher-order thalamic nucleus that coordinates multimodal sensory areas with the prefrontal cortex (PFC). Recent evidence suggests that PM also plays a distinct role in early postnatal life, promoting the anatomical maturation of recurrent PFC circuits through robust connections that are subsequently refined. However, whether this reflects a functional circuit mechanism underlying cognitive development is unknown. Here, we explored this hypothesis by permanently inactivating PM during early or late postnatal life in the marmoset monkey (*Callithrix jacchus*) and examining the consequence on PFC function and cognitive behavior. We employed MRI/CT-guided stereotaxic surgery to ablate the bilateral PM at either infancy (PD14; lesion: n=4) or adulthood (>18mo; n=2) and compared outcomes in adulthood to healthy controls (n=6). Using a homecage-integrated platform (CalliCog), marmosets performed a battery of touchscreen-based tasks designed to assess cognitive flexibility (reversal learning) and working memory (delayed match-to-sample task (DMTS) and delayed recognition span task (DRST)), two operations associated with PFC function. Concurrently, we recorded EEG from the epidural PFC via surgically implanted wireless implants and performed spectral analysis to compare neural activity during epochs of working memory. In summary, cognitive testing revealed that marmosets receiving early-life PM lesions exhibited a modest reduction in cognitive flexibility in reversal learning (p<0.05) but a severe reduction in the capacity to maintain working memory for >2 seconds in the DMTS (p<0.01). Conversely, working memory maintenance after adult lesions did not differ from controls (p>0.05), suggesting that cognitive dysfunction was developmentally regulated. Furthermore, EEG revealed a selective reduction in baseline gamma power (30-80 Hz) in the PFC following early life lesions compared to control (-3.2%; p<0.05), a known physiological correlate of working memory. These changes were associated with unique task-related neural signatures between lesioned and sham animals in the encoding and maintenance phases of the DMTS. These findings prove that PM plays a specific role in the postnatal development of the PFC and cognition in primates. Further studies of this mechanism may provide valuable insights into neurodevelopmental disorders in which this circuit is highly implicated.

Disclosures: J.T. Scott: None. **G. Gu:** None. **A.Y. Fan:** None. **J.A. Bourne:** None.

Poster

PSTR436: Development of Neural Systems

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.10/A73

Topic: A.08. Development of Neural Systems

Support: ZIAMH002920

Title: Cerebral lateralization of right hemisphere visual regions precedes lateralization of language and somatomotor regions in infants and young children

Authors: *S. J. GOTTS, S. C. MILLEVILLE, A. MARTIN;
Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD

Abstract: In adults, we have previously described two distinct forms of hemispheric specialization in the left versus right hemispheres (Gotts et al., 2013, PNAS), with lateralized left hemisphere regions showing a bias to interact with other left hemisphere regions ("Segregation") and right hemisphere regions showing a bias to interact with both hemispheres ("Integration"). Less is known about the developmental trajectory of brain lateralization, especially at the earliest ages. In the current study, we use fMRI data from the Lifespan Baby Connectome (Howell et al., 2019, Neuroimage) project to examine the lateralization of resting-state brain activity in sleeping infants and young children from birth through 5 years of age (N = 260 individuals, each with 11 minutes of resting-state fMRI data). We compare infant/child lateralization patterns directly to samples of adolescent data (ABCD, N=582) and adult data from the Human Connectome Project (N=1144). We find that patterns of right hemispheric lateralization in infants/children replicate older-aged lateralization patterns as early as 0-6 months (RH Integration, e.g. frontal eye fields) and 7-12 months (RH Segregation, e.g. dorsal and ventral visual streams). While some left hemispheric lateralization is observed as early as 0-6 months (e.g. left Heschl's gyrus, left posterior cingulate cortex), core language regions such as Broca's and Wernicke's areas do not emerge until after 2 years of age and fail to emerge through 5 years of age for somatomotor regions. The prominent presence of right hemisphere Segregation and left hemisphere Integration at the youngest ages also suggest that Segregation and Integration patterns are circuit- rather than hemisphere-specific.
Data use statement:Data and/or research tools used in the preparation of this abstract were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): [10.15154/1526487]. This abstract reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA.

Disclosures: S.J. Gotts: None. **S.C. Milleville:** None. **A. Martin:** None.

Poster

PSTR436: Development of Neural Systems

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.11/A74

Topic: A.08. Development of Neural Systems

Support: CIHR (PJT 399790)
Human Frontier Science Program Organization (CDA00009/2018 and RGY0072/2019)
SickKids Foundation and Canadian Institutes of Health Research (CIHR) – Institute of Human Development
Child and Youth Health (NI19-1132R)

Natural Sciences and Engineering Research Council of Canada (RGPIN-2017-06344) to MAC

Title: Investigating the role of the prelimbic cortex in developmental fear processing

Authors: *H. PREMACHANDRAN[1], M. MATTHIESEN[2], M. ARRUDA-CARVALHO[3]; [1]Psychology, Univ. of Toronto Scarborough, Scarborough, ON, Canada; [2]Toxicology, UNESP, Araraquara, Brazil; [3]Dept. of Psychology, Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: The rodent medial prefrontal cortex (PFC) undergoes substantial anatomical and synaptic changes in early development. The prelimbic cortex (PL) subregion of the PFC and its connections to the basolateral amygdala (BLA) play a crucial role in fear expression and retrieval in adult rodents. However, fear learning has been shown to be developmentally regulated, and some evidence suggests that younger rodents process fear in a PFC-independent manner. Since existing research on the role of the immature PFC in fear processing is sparse, we investigated the timing of PL and PL-BLA pathway recruitment for fear conditioning. We first used chemogenetics to inhibit the PL and PL-BLA pathway in infancy (postnatal day (P) 15) and adolescence (P30) during fear training and tested for fear retrieval and contextual fear 24h later. We found that while infant mice were unaffected by this manipulation, adolescent mice showed impaired fear retrieval when the PL and PL-BLA pathway were inhibited during fear conditioning. Additionally, using a combination of optogenetics and whole-cell patch clamp electrophysiology, we found that while fear conditioning in P30 mice led to an increase in AMPA:NMDA ratios in PL-BLA synapses, P15 mice showed an absence of fear-induced synaptic plasticity in the same pathway. Overall, our results indicate that the PL and PL-BLA pathway are only recruited to support fear encoding between infancy and adolescence. Understanding the contribution of the PL-BLA pathway to early fear processing yields valuable insight into circuit maturation and the mechanisms of emotional learning at key developmental stages.

Disclosures: H. Premachandran: None. **M. Matthiesen:** None. **M. Arruda-Carvalho:** None.

Poster

PSTR436: Development of Neural Systems

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Program #/Poster #: PSTR436.12/A75

Topic: A.08. Development of Neural Systems

Support: R01NS120832
NSF 1707352
U01NS099709

Title: Developmental perturbation of the locus coeruleus results in significant behavioral changes in adults

Authors: *A. D. SILVAGNOLI[1], M. O. TREE[2], U. HOCHGESCHWENDER[3];
[1]Central Michigan Univ., Mt. Pleasant, MI; [2]Central Michigan Univ., Mount Pleasant, MI;
[3]Neurosci., Central Michigan Univ., MT Pleasant, MI

Abstract: The locus coeruleus (LC) is a key producer of catecholamines and the main producer of norepinephrine in the CNS. The LC also maintains significant projections to areas known for their importance in cognitive function. Studies on the LC have linked its activity with behavioral modification at the neuronal and network level. Dysregulation of this nucleus is strongly correlated with developmental disorders such as attention deficit hyperactive disorder (ADHD) and autism spectrum disorder (ASD). Evidence from humans, non-human primates, and rodents indicates the significant impact of LC dysfunction on cognition and broader network dynamics. However, investigating LC's role in development of cognitive networks yields conflicting results. Here we propose to investigate how LC dysfunction during development may lead to network-based changes associated with developmental disorders such as ADHD and ASD. Employing non-invasive bioluminescent optogenetic (BL-OG) techniques in conjunction with recombinase-based genetic strategies and adeno-associated viral transductions, we selectively manipulate the LC during critical development periods to assess if early perturbation of LC to prefrontal circuits leads to enduring circuit level changes in adult animals. Behavioral and electrophysiological studies will show if changes correspond to phenotypes reminiscent of the alterations seen in individuals symptomatic for ADHD and ASD.

Disclosures: A.D. Silvagnoli: None. **M.O. Tree:** None. **U. Hochgeschwender:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.13/A76

Topic: A.08. Development of Neural Systems

Title: Gut Microbiome and Dynamic Functional Connectivity in Infants

Authors: *A. KAUR[1], W. GAO[2], H. CHEN[2], A. M. ALEX[1], M. AZCARATE-PERIL[3], A. THOMPSON[3], C. PROPPER[3], M. A. STYNER[3], A. L. CARLSON[4], R. C. KNICKMEYER[1];
[1]Inst. for Quantitative Hlth. Sci. and Engin., Michigan State Univ., East Lansing, MI; [2]Biomed. Imaging Res. Inst., Cedars Sinai Med. Ctr., Los Angeles, CA; [3]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Univ. of California San Diego, La Jolla, CA.

Abstract: Recent attention has been drawn to the concept of holobionts, emphasizing the human body as a host to diverse microorganisms. Of particular interest is the gut microbiome, which has been found to significantly influence cognitive development via the gut-brain axis. Further, the amygdala, a crucial brain region involved in processing fear, stress, and social cognition, has been implicated in mediating gut microbiota-behavior associations. While past research links the amygdala's dynamic function connectivity to neurodevelopmental disorders, further exploration

is needed regarding the linkage between the gut microbiome metrics and dynamic changes in the amygdala's connectivity. Thus, this preliminary study aims to assess the relationship between alpha diversity measures at birth and temporal variability in the amygdala at one year of age in 24 infants. Functional and anatomical data were preprocessed using a flexible preprocessing pipeline in CONN 22.a, which included removing initial scans, realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation, and MNI-space normalization to 12-month template, smoothing, and denoising. Next, Fisher-transformed bivariate correlation coefficients from a weighted general linear model were estimated using a sliding time window analysis to assess the temporal variability between the amygdala and the voxels in the rest of the brain. At the group level, for each voxel and amygdala as seed, a separate general linear model was estimated, with temporal variability at this voxel as the dependent variable and alpha diversity indices (Pielou's evenness and Faith's PD) as independent variables while controlling for age, gender, and family income. Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold and a familywise corrected p-FDR < 0.05 cluster-size threshold. The results showed that greater Faith's PD correlated with increased temporal variability of the seed region (right lateralized amygdala) with right lateralized supramarginal gyrus (T(18)=5.84; cluster size: 32) and left lateralized post central gyrus (T(18)=5.65; cluster size: 21). These preliminary findings offer valuable insights into the gut-brain axis during early human development, underscoring the necessity for further research to investigate whether microbiome-related changes in brain dynamics influence somatosensory integration and cognitive functions.

Disclosures: A. Kaur: None. **W. Gao:** None. **H. Chen:** None. **A.M. Alex:** None. **M. Azcarate-Peril:** None. **A. Thompson:** None. **C. Propper:** None. **M.A. Styner:** None. **A.L. Carlson:** None. **R.C. Knickmeyer:** None.

Poster

PSTR436: Development of Neural Systems

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Topic: A.08. Development of Neural Systems

Support: NIH Grant MH116527
NIH Grant RF1AG082938

Title: Enhanced multimodal prediction of infant brain cognition: domain transfer from adult data to ages 0-36 Months

Authors: *T. LI[1], W. YIN[2], Z. WU[3], G. LI[4], H. ZHU[5], W. LIN[6];
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Abstract: Background: Accurately predicting cognitive development in infants remains a significant challenge due to its limited sample size and intricate nature of neural processes. Leveraging domain transfer from extensive adult datasets, such as the UK Biobank, presents a promising avenue, particularly aiding in incorporating high-dimensional biomarkers, such as functional connectivity. However, substantial obstacles arise from data heterogeneities, including age disparities, ethnic variations, differing imaging protocols, and diverse intelligence assessment. In this study, we incorporate two pre-trained functional models from adult datasets and integrate them with infants' structural measures to enhance cognition prediction. **Method**: A total of 144 infants (15.10 ± 7.47 months) and both T1-weighted MRI and resting-state functional MRI scans were included in this study. The Mullen Scales of Early Learning (MSEL) composite scores were assessed within 12 months after the MRI measurement, which include 5 domains, the gross motor, fine motor, receptive language, expressive language and visual reception. The composite score and all subdomains were standardized into age-invariant t-scores and dichotomized into high and low cognitive groups. Meanwhile, brain anatomical features including surface area, cortical thickness, and myelin (T1-T2 ratio) were extracted. Resting-state MRI (rfMRI) connectivity were extracted between pairs of brain regions. Two pre-trained rfMRI-based regression models were extracted from the UK Biobank and Adolescent Brain Cognitive Development Study (ABCD) data in prediction of the fluid intelligence score, which were transferred to the infant data and combined with structural measures to predict the MSEL scores in the upcoming 12 months using a large variety of regression and machine learning models. **Result**: The area under the curves (AUCs) of the fine motor score prediction was improved from 0.645 (± 0.046) to 0.684 (± 0.044) by incorporating the transferred models from adults. Besides, important contributing biomarkers identified in prediction of the fine motor score in the next 12 months include the surface areas of left fusiform, left lsthmus insula, left pars orbitalis, left supra marginal, left transverse temporal and left post central regions, and the cortical thicknesses of the left rostral anterior cingulate, left lateral occipital and left pericalcarine regions. **Conclusion**: This enhancement underscores the potential of cross-population predictive models in overcoming the challenges posed by small and heterogeneous infant datasets.

Disclosures: T. Li: None. **W. Yin:** None. **Z. Wu:** None. **G. Li:** None. **H. Zhu:** None. **W. Lin:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.15/A78

Topic: A.08. Development of Neural Systems

Title: Histochemical Indicators of Inflammation and Oxidative Stress in Tissues Adjacent to Craniopharyngioma boundies

Authors: *C. MARTÍNEZ ZAMORA[1], L. MARIN-CASTAÑEDA[2], G. GONZALEZ-GARIBAY[2], S. VIDAL[2], A. LOPEZ, Sr.[2], M. TENA SUCK[2], C. R. OSORNIO[2];

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Abstract: Craniopharyngiomas (CPs) are epithelial tumors of the sellar region characterized by high survival rates yet frequently recurring, particularly in pediatric patients. Hypothalamic compromise, tumor recurrence, and multiple treatments result in clinical deterioration and impaired quality of life. In this work, we analyzed immunohistochemical profiles of different factors involved in toxic pathways that promote inflammation and oxidative damage in craniopharyngioma tumors. We also examined the ultrastructure of these invasive processes and analyzed the oil-like fluid content. Twenty-eight patients were included in the study, 15 of whom presented recurrence, while the other 13 did not; 23 patients also showed invasion of adjacent brain tissue correlated with gender ($p=0.044$), inflammation ($p=0.048$), presence of Rosenthal fibers ($p<0.00001$). Dystrophic calcification under invasive conditions tested positive for recoverin, lactate dehydrogenase (LDH), tumor necrosis factor alpha (TNFα), gamma-interferon-inducible protein 16 (IFI16), and nuclear factor erythroid 2 (NrF2); and negative for perilipin, nitroturoisine, endothelial NOS, tumor necrosis factor gamma (TNFγ) hypoxia-inducible factor 1-alpha (HIF1α), GSK3β, and glucose transporter type 4 (Glu-4). The mechanisms underlying wet keratin invasion were positive for recoverin, LDH, NFκB, TNFα, IFI16, and Nrf2; and negative for perilipin, TNFγ, nitrotyrosine, e-NOS, HIF1α, and GSK3β. Single-cell infiltration pathways were positive for LDH, thioredoxin reductase 1 (TrxR1), TNFα, nitrotyrosine, HIF1A, endothelial NOS, GSK3β, Glut-4, Nrf2, CD71, and perilipin. Considering all these findings, we conclude that tumor invasion into brain tissue activates several factors at the boundary, likely leading to inflammation and oxidative stress through the release of oil machinery fluids caused by basal membrane rupture.

Disclosures: C. Martínez Zamora: None. **L. Marin-Castañeda:** None. **G. Gonzalez-Garibay:** None. **S. Vidal:** None. **A. Lopez:** None. **M. Tena Suck:** None. **C.R. Osornio:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.16/A79

Topic: A.08. Development of Neural Systems

Title: Conditioning of fetal hypothalamic nuclei by gestational, high fat diet: An anatomical screening

Authors: *N. GALINDO SOLANO[1,2], G. DÍAZ-OLIVARES[3], X. TREJO-VILLARREAL[4], G. REA-PALOMINO[4], G. GUTIERREZ-OSPINA[5];
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Abstract: Traditionally, it is believed that the states considered pathophysiological, manifested in adulthood, result from the negative impact that chronic allostatic load has on the body from birth. However, there is evidence supporting that postnatal pathophysiological manifestations have their roots in prenatal life due, in part, to the embryo/fetus's ability to register adverse events experienced during gestation and translate them into a "phenotypic memory." This ability, it is thought, allows fetuses to "make guesses" about the types of conditions they will face from birth, conditioning their trajectory of pre- and postnatal development and maturation. We consider this situation underlies obesity. Therefore, in our work, we have devised a strategy aimed at providing empirical evidence in favor of the aforementioned possibility, using the hypothalamic brain centers responsible for hunger cycle regulation as witnesses, and embryos of rats exposed to a high-fat diet as experimental units. The results obtained so far suggest that gestational exposure to this diet up to one day before birth decreases reproductive efficiency, modifies the intersexual ratio, induces a state of placental insufficiency, evidenced by a decrease in placental weight and a drop in fetal weight and length, as well as a change in hypothalamic neurons associated with hunger regulation. Reproductive efficiency and intersexual ratio are partially normalized, along with the rest of the mentioned parameters, when mothers consume diets enriched in fats supplemented with vitamins B1, B6, and B2. The above is consistent with previous studies showing that gestational consumption of methyl-donor compounds partially protects fetuses from the harmful effects of inadequate gestational nutritional environments.

Disclosures: N. Galindo Solano: 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.; Programa de Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México (UNAM) and has received CONAHCYT fellowship 748035., Programa Institucional de Obesidad y Diabetes del Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México (UNAM). **G. Díaz-Olivares:** 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.; Programa de Maestría en Ciencias (Neurobiología), Universidad Nacional Autónoma de México (UNAM) and has received CONAHCYT fellowship 1321212. **X. Trejo-Villarreal:** None. **G. Rea-Palomino:** None. **G. Gutierrez-Ospina:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.17/B1

Topic: A.08. Development of Neural Systems

Support: 5R01MH124695
SFARI Bridge to Independence award

Title: Striatal output regulates the postnatal maturation of mPFC circuits

Authors: T. DEEMYAD[1], M. JANECEK[2], Y.-C. SHIH[3], ***R. PEIXOTO**[3];
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Abstract: The dorsomedial prefrontal cortex (dmPFC) is interconnected with the basal ganglia (BG) through large-scale circuit loops that regulate critical motor and cognitive functions. In mice, these circuits undergo extensive postnatal maturation with marked changes in neural activity and expansion of synaptic connectivity. While cortical activity is known to regulate the development of downstream striatal circuits, the role of the basal ganglia in cortical maturation remains unknown. Here, we used mesoscale two-photon microscopy and whole-cell electrophysiology to examine whether striatal output during early postnatal development impacts the maturation of upstream dmPFC circuits. We found that ablating spiny projection neurons of the direct or indirect pathways of the striatum during the first two postnatal weeks causes bidirectional changes in dmPFC neural activity, similar to what is observed in mature circuits. In addition, these manipulations alter the maturation of synaptic connectivity of dmPFC layer 2/3 pyramidal neurons, shifting the balance of excitation and inhibition of cortical circuits. These findings demonstrate that striatal output regulates the activity of cortical circuits during early postnatal development and suggest a regulatory role of the basal ganglia in the establishment of cortical circuits.

Disclosures: T. Deemyad: None. **M. Janecek:** None. **Y. Shih:** None. **R. Peixoto:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.18/B2

Topic: A.08. Development of Neural Systems

Support: FRIPRO Grant 324305

Title: Hippocampal Cajal-Retzius Cells Receive Inputs From Several Extrahippocampal Areas

Authors: ***K. MOAN**[1], R. P. MACHOLD[2], G. QUATTROCOLO[1];
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Abstract: Cajal-Retzius (CR) cells are an early born, reelin-expressing, excitatory neuronal population located in the cerebral cortex and hippocampus. They serve a critically important function during the first postnatal week (P0-P7) of cortical development in the mouse. While CR

cells largely die off in the neocortex after the second postnatal week, in hippocampus, they persist throughout postnatal development and even into adulthood. During this time, they are integrated in the CA1 network, and our recent work (Glærum et al. 2024) has showed that their persistence in the hippocampus is critical for the development of hippocampal circuitry. However, the input and output connectivity of CR cells remains poorly understood, hindering our appreciation of the role of these cells in postnatal hippocampal development. The aim of this project is therefore to examine the long-range projections to, and from, hippocampal CR cells. To achieve this, we are combining the use of transgenic mouse lines, viral vectors and state-of-the-art microscopy techniques, such as confocal and light-sheet microscopy. Our preliminary results indicate that CR cells receive long-range inputs from several extrahippocampal areas including entorhinal cortex, thalamus, and the midbrain. This suggests that CR cells could act as an intermediate target of most, if not all, afferent fibers reaching the hippocampus during early development. Interestingly, mouse whole-brain imaging from several postnatal ages reveals almost no projections from hippocampal CR cells to extrahippocampal areas. This implies that hippocampal CR cell projection is restricted to local hippocampal neurons, and potentially layer 1 of neighboring cortical areas. Altogether these data shed new light on the nature of hippocampal CR cell connectivity and challenge previous hypotheses regarding the output of CR cells.

Disclosures: K. Moan: None. **R.P. Machold:** None. **G. Quattrocolo:** None.

Poster

PSTR436: Development of Neural Systems

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Program #/Poster #: PSTR436.19/B3

Topic: A.08. Development of Neural Systems

Support: ANR-16-CONV-0001
ANR_HIPPODEVINAU_U1249

Title: Early developmental transition in developing hippocampus CA1 is disrupted in two mouse models of ASD

Authors: *M. R. RATSIFANDRIHAMANANA[1,2], R. DARD[3], A. BAUDE[4], R. A. COSSART[5], E. DAUCÉ[2,6], M. A. PICARDO[4];
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Abstract: The mature hippocampus is a cognitive structure which creates cognitive maps, a function altered in Autism Spectrum Disorders (ASD) (Banker et al, 2021). In contrast to the mature stage, the early developing hippocampus CA1 acts as a sensory area that integrates information. Indeed, early in the development, the activity in CA1 is triggered by external information, including spontaneous movements, which are later integrated internally (Dard et al. 2022). We hypothesized that early disruptions of this transition could lead to cognitive deficits later in the development. To answer this question, we asked whether this developmental transition is altered in ASD.We used two genetic mouse models of ASD: Shank3 and Cntnap2, to identify the early changes in the developing hippocampus on a functional and anatomical level. First, we performed in vivo calcium imaging in the pyramidal layer of CA1 in unanesthetized pups aged P6 to P12 to quantify the neuronal response to external sensorimotor inputs. Our results show a reduction of the neuronal response to the movement in mouse models of ASD. We used mutual information to validate whether this reduced neuronal response is associated to a misrepresentation of the sensorimotor inputs within the neuronal activity. We found that in both ASD models, mice displayed a different pattern of mutual information which is associated to a difference in the representation of the movement. These results show impairments of in vivo neuronal dynamics in both ASD mouse models during the transition between the first and the second postnatal week. In addition, our analysis shows that the internalization of the movements is significantly altered in both models. Altogether, these early disruptions might lead to the apparition of autistic-like phenotypes, including hippocampal cognitive deficits at adult stage (Paterno et al, 2021; Wang et al, 2011).

Disclosures: M.R. Ratsifandrihamanana: None. **R. Dard:** None. **A. Baude:** None. **R.A. Cossart:** None. **E. Daucé:** None. **M.A. Picardo:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.20/B4

Topic: A.08. Development of Neural Systems

Support: ROGER DE SPOELBERCH Prize 2021

Title: Development of intrinsic hippocampal dynamics in health and disease

Authors: *C. SAN MARTÍN, P. HUYNH, A. CARABALONA, A. BAUDE, M. PICARDO, R. COSSART;
Inst. de Neurobiologie de la Méditerranée (INMED), INSERM, Aix-Marseille Univ., Marseille, France

Abstract: Cognitive brain functions like memory and navigation are supported by the ability of the hippocampus to generate orderly neural representations of events and facts in the form of discrete cell assemblies that activate in a sequential manner. In the adult brain, hippocampal cell

assembly sequences arise from intrinsic neuronal dynamics embedded in local circuits onto which extrinsic multi-sensory input is mapped. In contrast, in early developmental stages, hippocampal dynamics are exclusively driven by bottom-up extrinsic input (Leprince et al., 2022). Interestingly, during the second postnatal week, the rise of somatic inhibition transitorily disengages neuronal dynamics from extrinsic input in the CA1 region of the mouse hippocampus (Dard et al., 2022). We hypothesize that the development of inhibitory neurons initiates intrinsic circuit dynamics, thus inaugurating a critical window in hippocampal function. Using a combination of mouse genetics and *in vivo* calcium imaging, we aim to test whether the rise of PV+ or CCK+ interneurons, the two main sources of somatic inhibition in the CA1 region, triggers the development of intrinsic dynamics in hippocampal circuits.

Disclosures: C. San Martín: None. **P. Huynh:** None. **A. Carabalona:** None. **A. Baude:** None. **M. Picardo:** None. **R. Cossart:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.21/B5

Topic: A.08. Development of Neural Systems

Support: ERC HOPE

Title: The clonal origin of hippocampal cell assemblies

Authors: *A. CARABALONA[1,2], C. FILIPPI[2], J. LIVET[3], J.-C. PLATEL[2], R. A. COSSART[2]; [1]INMED, vandoeuvre les nancy cedex, France; [2]INMED INSERM U1249, Aix-Marseille university, France; [3]Inst. de la Vision, Paris, France

Abstract: The hippocampus provides a cognitive map supporting navigation, associative learning, and memory. This function is supported by the ability of hippocampal circuits to produce sequences of cell assembly activation arising from the interaction between external contextual inputs and internally-generated preconfigured dynamics. Recent work suggests that internally preconfigured assemblies, shaped by their developmental origin, are the basic modules of hippocampal function. Here we combine lineage analysis with *in vivo* calcium imaging to show that a significant proportion of CA1 cell assemblies coordinate the activity of clonally-related neurons.

Disclosures: A. Carabalona: None. **C. Filippi:** None. **J. Livet:** None. **J. Platel:** None. **R.A. Cossart:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.22/B6

Topic: A.08. Development of Neural Systems

Support: ERC Grant HOPE
ROGER DE SPOELBERCH Prize 2021
BETTENCOURT

Title: Development of hippocampal sequences and assemblies

Authors: *E. LEPRINCE[1,2], C. FILIPPI[1], J. MAJNIK[1], M. MANTEZ[1], J.-C. PLATEL[1], M. BOCCHIO[3], R. COSSART[1];
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Abstract: The hippocampus serves multiple cognitive functions, including navigation and memory. These functions rely on its ability to produce sequences of neuronal assemblies, creating cognitive maps that depict the connections between previously encountered locations or experiences. Cognitive hippocampal maps rely on two mechanisms, one that is allocentric and requires environmental landmarks and the other that is self-referenced, or egocentric. Remarkably, in the adult CA1 region, these two forms of representation segregate into two different subcircuits along the radial axis with deep CA1 principal cells being more anchored to external landmarks (external representation). In contrast, superficial ones would convey self-referenced information (internal representation). However, this ability to internally generate neuronal activity detached from environmental inputs in the adult hippocampus differs from the developing one, which primarily relies on bottom-up sensorial information. Hippocampal neurons start encoding locations along animals' paths as early as the third postnatal week. By the fourth week, compressed theta sequences develop, representing the animal's trajectory in a cued environment, suggesting CA1 dynamics internalisation. This could indicate that the subcircuits contributing to the balance between external and internal representations would be shaped during this critical post-natal period. Here we compared the developmental timelines for the emergence of internal and external hippocampal representations in the deep and superficial CA1 principal layer using longitudinal two-photon calcium imaging from head-fixed mice free to run on an empty or a cued self-paced treadmill between postnatal days 20 and 27.

Disclosures: E. Leprince: None. **C. Filippi:** None. **J. Majnik:** None. **M. Mantez:** None. **J. Platel:** None. **M. Bocchio:** None. **R. Cossart:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.23/B7

Topic: A.08. Development of Neural Systems

Support: ANR AMIDEX CIRCUITPHOTONICS

Title: Imaging neuronal activity in vivo

Authors: *S. BRUSTLEIN, J.-C. PLATEL, R. A. COSSART;
Aix Marseille Univ., INSERM U1249, Marseille, France

Abstract: Mapping the long-term dynamics of neuronal activity, at a large scale, with single-cell resolution, in behaving animals, is at the heart of Neuroscience research. The ongoing revolution in functional imaging, with new technologies in photonics and probe design, now opens the possibility to explore the emergence and plasticity of functional circuits during development and their dynamics. To meet this challenge, we have created CIRCUITPHOTONICS, a new platform dedicated to the *in vivo* imaging of neuronal dynamics in rodents and non-human primates. The originality of the platform lies in the deployment and co-conception of innovative imaging technologies beyond the state-of-the-art, with three main axes: (1) chronic minimally invasive deep brain imaging; (2) fast imaging of neuronal membrane potential dynamics; (3) and non-human primates imaging, in particular marmoset, a promising model for biomedical research. The poster presented here highlights examples of experiments conducted at the Institute of Mediterranean Neurobiology, focusing on several key areas such as: (i) mapping the plasticity of brain circuits, the same cells can be imaged from early development into adulthood using 3-photon/2-photon calcium imaging and cells of interest can be targeted simultaneously thanks to a photostimulation module equipped with a spatial light modulator; (ii) visualizing the dynamics of neuronal membrane potential *in vivo*, thanks to genetically engineered voltage-sensitive indicators and an ultra-fast, ultra-low noise, random access two-photon microscope equipped with acousto-optic deflectors and; (iii) recording calcium imaging brain activity in freely moving rodents, using a 2-photon endoscope.

Disclosures: S. Brustlein: None. **J. Platel:** None. **R.A. Cossart:** None.

Poster

PSTR436: Development of Neural Systems

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR436.24/B8

Topic: A.08. Development of Neural Systems

Support: Reynold Innovative Spinal Electrical Stimulation Program

Title: The RISES System: An Innovative Activity-Based Closed-Loop Framework for Spinal Cord Injury Rehabilitation and Recovery with Immediate Effects of Transcutaneous Spinal Cord Stimulation: A Methodological Pilot Study.

Authors: *S. MADARSHAHIAN[1], T. GUERRERO[1], P. AUNG[1], K. GUSTAFSON[2], D. JOHNSON[3], M. KHANTAN[1], N. GRAMPUROHIT[4], M. MULCAHEY[3], A. NAPOLI[1], M. SERRUYA[1];
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Abstract: Electrical spinal cord stimulation (SCS) has shown promise in enhancing pathway rewiring and functional recovery in people with spinal cord injury (SCI). Given the complexity of spinal circuitry and the heterogeneity in impairment levels and conditions of individuals living with SCI, there may be an advantage to having a closed-loop system that dynamically adjusts stimulation parameters based on sensor signatures of each unique individual and each unique task. We piloted the safety and feasibility of the Reynold Innovative Spinal Electrical Stimulation (RISES) technology in a feasibility clinical trial including four SCI patients. RISES is a personalized, task-specific non-invasive stimulation system that enables real-time modulation of stimulation parameters during activity-based training. Safety outcomes included adverse events (AEs) and skin integrity, vital signs, pain, and fatigue. The clinical trial included both open-loop and closed-loop sessions of transcutaneous spinal cord stimulation (tSCS). We compared neurophysiological, kinematic, and kinetic variables, in response to different electrode placement setups and stimulation parameters such as amplitude, frequency, pulse-width, and stimulation type (Burst, No-Burst). Statistical comparisons were obtained using a mixed-linear model with statistical significance assessed at a p-value of 0.05. Our results showed no serious adverse events, with skin integrity unaffected. Although fatigue levels increased significantly with sessions (post-session > mid-session > pre-session), when comparing open-loop and closed-loop blocks, no significant differences in setup time, vital signs, pain, or fatigue were detected. The average total-stimulation-on duration per task was significantly longer in open-loop sessions (468 sec) compared to closed-loop (411 sec). Our findings indicated that:1) Different Configurations engaged different spinal pathways 2) During stimulation at rest and during isometric task performance, firing rates of some motor units in the distal tibialis anterior muscle increased and were sustained while the stimulation was applied; and 3) closed-loop tSCS led to a more stable standing posture compared to no stimulation, as measured by reduced head IMU sensor deviations. Our current results demonstrate the safety and feasibility of the RISES system and that parameter optimization is crucial for effective clinic use.

Disclosures: S. Madarshahian: None. **T. Guerrero:** None. **P. Aung:** None. **K. Gustafson:** None. **D. Johnson:** None. **M. Khantan:** None. **N. Grampurohit:** None. **M. Mulcahey:** None. **A. Napoli:** None. **M. Serruya:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.01/B9

Topic: B.03. Ion Channels

Support: ISF Grant 1384/19

Title: Axonal spike propagation velocity unaffected by myelination in developing mouse neocortex

Authors: *O. KOTLER, Y. KHRAPUNSKY, I. A. FLEIDERVISH;
Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: Myelination occurs relatively late in the course of postnatal cortical development, marking one of the final milestones in the maturation of neuronal circuits. In immature, non-myelinated axons, voltage-gated Na^+ channels - critical for initiating action potentials (APs) and facilitating their continuous propagation - are believed to be evenly distributed along the length of the axon. In axons of mature cortical neurons, Na^+ channels are selectively localized to the axon initial segment (AIS) and nodes of Ranvier, where the axolemma is exposed to the extracellular space. The internodal segments are encased by a multilayered sheath of myelinating oligodendroglial processes, which augments their effective resistance while diminishing their effective capacitance. The propagation in myelinated axons is widely believed to be "saltatory," meaning that the AP jumps from node to node of Ranvier, making the process faster and more energy-efficient than in non-myelinated fibers. Here, we directly measured AP propagation velocity in axons of L5 pyramidal neurons using a combination of somatic whole cell and axonal loose patch recordings in brain slices of immature (P6-P7) and mature (P25-P45) mice. Concurrently, we assessed the distribution of Na^+ flux within the axons by measuring fluorescence changes of a Na^+-sensitive dye, SBFI, elicited by trains of five APs at 200 Hz. Our measurements revealed no significant difference in AP propagation velocity between immature (0.33 ± 0.02 m/s, $n = 11$) and mature (0.31 ± 0.02 m/s, $n = 10$) cortical axons across the analyzed range of 100-350 µm from the soma. In mature mouse slices, the first nodes of Ranvier were revealed by the characteristics of their Na^+ transients within 95-110 µm of the soma, and the subsequent nodes were spaced at regular intervals of 20-30 µm. Consistent with our prior observation of Na^+ influx limited to nodes of Ranvier, we detected no Na^+ influx within the myelinated internodes. In contrast to mature neurons, immature cortical axons exhibited Na^+ influx along their entire length. Notably, we observed spots of high Na^+ influx at locations where collateral branches originate from the main axonal trunk. Interestingly, during AP propagation, immature axons exhibited slightly higher Na^+ charge transfer per unit length (73.9 ± 6.3 fCu/µm, $n=4$) than mature, myelinated axons (44.1 ± 5.7 fCu/µm, $n=4$; $p=0.013$). Our findings indicate that, in contrast to the peripheral nervous system, myelination in cortical axons does not enhance signal speed but reduces the energy costs of electrical signaling by ~40%.

Disclosures: O. Kotler: None. **Y. Khrapunsky:** None. **I.A. Fleidervish:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.02/B10

Topic: B.03. Ion Channels

Title: Complex allelic interactions shape presentation of behavioral hyperexcitability in Drosophila Na_Vchannel mutants

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Abstract: Complex allelic interactions shape presentation of behavioral hyperexcitability in*Drosophila* NaV channel mutantsHusnain Riaz and Atulya IyengarDepartment of Biological Sciences, The University of AlabamaVoltage-gated sodium (NaV) channels are crucial for action potentials generation in mostneurons. There are nine distinct NaV channel genes in vertebrates, while *Drosophilamelanogaster* possess a single orthologous NaV channel gene, *paralytic (para)*. Remarkably,*Drosophila para* mutant alleles display a diverse range of phenotypes reminiscent ofhuman channelopathies. A loss-of-function mutation, $para^{ts1}$, display paralysis at hightemperatures. In $para^{bss1}$, a gain-of-function mutation, mechanical shock triggers astereotyped sequence of spasm and paralysis (bang sensitivity). Another gain of functionalleles, $para^{Swd}$, shows spontaneous seizure exacerbated by elevated temperature. Twoalleles, $para^{GEFS}$ and $para^{DS}$, orthologous to epilepsy-linked point mutations, show heat-induced seizures. Notably, $para^{GEFS}$ is a gain-of-function mutation, and $para^{DS}$ is a loss-of-function mutation. We explored intragenic interactions between *para* alleles to understandtheir impact on behavior and seizure susceptibility. Specifically, we created heteroalleliccombinations of *para* mutants and observed corresponding hyperexcitable behaviors in anautomated high-throughput fashion. These heterozygous lines were subjected to anelevated temperature ramp (20-40 ºC) using Peltier temperature-controlled stage. Anautomated video recording and tracking system, IowaFLI tracker, monitored locomotioncharacteristics of individual flies. We found striking intragenic interactions across diRerent*para* mutants, most involving the allele $para^{Swd}$. Only 10% of $para^{Swd}$/+ heterozygotesexhibited heat-induced spasms. However, when $para^{Swd}$ was combined with loss offunction allele $para^{DS}$ and $para^{ts1}$, 100 % of flies showed these being heat-induced spasm.Interestingly, only $para^{Swd}/para^{DS}$ showed reduced average walking velocity to 2.6 mm/s (vs$para^{Swd}/para^{ts1}$ and $para^{Swd}$/+ 4.4 mm/s). Gain-of-function alleles, $para^{GEFS}$ and $para^{bss1}$modified the heat-induced seizure phenotype in $para^{Swd}$ in distinct ways. All $para^{Swd}/para^{GEFS}$mutants experienced spasms, while $para^{Swd}/para^{bss1}$ mutants did not exhibit any heat-induced spasm. Neither gain of function alleles aRected walking velocities. These findingsilluminate the complex genetic interactions that underlie heat-induced seizuresusceptibility, contributing to a deeper understanding of how particular combinations ofNaV channel mutations lead to specific neurological phenotypes.

Disclosures: H. Riaz: None. **A. Iyengar:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

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National Natural Science Foundation of China 32130044
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Title: Scn2a deletion in ventral tegmental area dopaminergic neurons causes dopamine system hypofunction and autistic-like behaviors

Authors: *L. LI[1], Q. HUANG[1], J. HU[1], W. KE[1], Y. ZHUO[3], Q. HE[1], Y. XIAO[1], W. WANG[1], T.-L. CHENG[1], F. GUO[1], J.-T. YU[2], Y. LI[3], B. LI[1], Y. SHU[1];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental problem linked to various mutations, with *SCN2A* as a high-risk gene, but its precise contribution to pathogenesis remains obscure. *SCN2A* encodes the voltage-gated Na^+ channel (Na_V) 1.2 and promotes action potential (AP) generation and propagation in many types of neurons. Here we employ RNAscope combined with immunohistochemistry techniques and find that *Scn2a* is the dominant Na_V isoform in dopaminergic neurons (DANs) in mouse ventral tegmental area (VTA). $Na_V1.2$ immunosignals accumulates at the axon initial segments of DANs across developmental stages. Genetic deletion of *Scn2a* from VTA DANs using CRISPR/Cas9 system dramatically reduces their spontaneous firing frequency and the AP amplitude and maximal depolarization rate in midbrain slices. Using patch-clamp recording from nucleated patches and isolated axon blebs of VTA DANs, we reveal that $Na_V1.2$ contributes largely to Na^+ currents (ranging from 46-71%) along the somato-axonal axis. Remarkably, this focal loss of *Scn2a* causes repetitive circular locomotion and impaired social novelty, along with hyperactivity and insufficient anxiety. Using fiber photometry, dopamine release in the nucleus accumbens during social interactions is diminished in mice with focal *Scn2a* loss. Acute treatment with low dose of levodopa/benserazide is able to alleviate non-motor behavior deficits. Together, the results demonstrate that *Scn2a* deletion in VTA DANs alone impairs dopaminergic signaling and causes autistic-like behaviors, and importantly our findings also provide a potential pharmacotherapy through dopamine replacement for ASD cases with dopamine system hypofunction.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

Support: NIH R01MH124351 (FL)
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Title: Unveiling A Molecular Nexus of Neuropsychiatric Disorder: Newly Identified Protein Interactor of Nav1.6 In Neuroprotection

Authors: *N. GOODE[1], T. BAUMGARTNER[2], A. K. SINGH[3], L. KOFF[4], J. DI RE[5], J. SINGH[6], S. MOHANTY[6], G. GOLOVKO[7], F. LAEZZA[8];
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Abstract: Neuropsychiatric disorders (NDs) significantly impact the well-being of individuals by negatively affecting their overall health and productivity. Despite evidence pointing to genetic, environmental, and epigenetic factors as common key factors in the etiology, progression, and treatment of NDs, there is still inadequate knowledge on the molecular mechanisms that confer resilience to these disorders. In previous studies, we identified the voltage-gated Na+ channel Nav1.6 as a mediator of neuroplasticity induced by environmentally enriched (EC) or isolated (IC) conditions which are used as models for resilience and vulnerability. Protein-protein interactions are essential mediators of Nav1.6 channel function and the impact of EC/IC conditions on the relative composition of the Nav1.6 interactome is unknown. Based on this, we recently investigated the Nav1.6 protein interactome under EC and IC conditions to identify auxiliary proteins that may confer resilience or vulnerability to NDs in the hippocampus and striatum. To determine the impact of the EC/IC behavioral paradigm on the composition of the Nav1.6 channel macromolecular complex, we housed rats (n= 24; 6 males and 6 females per condition) in environmentally enriched (EC) and isolated conditions (IC) for 30 days. We used immunoprecipitation and nanoLC/MS/MS to investigate the proteome of Nav1.6 in these rats. We identified 88 and 32 differentially expressed protein interactors of Nav1.6 in the striatum and hippocampus of EC/IC male rats, respectively. Ingenuity Pathway Analysis of the differentially expressed protein interactors revealed EIF2 signaling, eukaryotic translation initiation, and regulation of eiF4 and p70S6K signaling pathways as the top 3 ingenuity canonical pathways. Following this, we selected one of the top 5 differentially expressed interactors for further investigation. Using immunoprecipitation and confocal imaging, we validated the interaction between Nav1.6 and the selected interactor. Additionally, we used electrophysiology to investigate the functional contribution of the selected interactor to Nav1.6 channel activity. Preliminary data shows that the selected interactor significantly reduces Nav1.6 peak current density, as well as the channel's long-term inactivation and use-dependency without considerably impacting the voltage-dependence of Nav1.6 activation and inactivation. The results of this study offer valuable information on a new molecular target with potential for the development of novel neurotherapeutics.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

Support: Grant of Frontiers of Sciences, CONAHCYT (F-2023-G-77)

Title: Assessment of venom of Centruroides exilicauda on voltage-gated ion channels from mice dorsal root ganglion neurons

Authors: *D. HUERTA-GONZALEZ[1], N. CARAM-SALAS[2], E. LUIS[3];
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Abstract: Some scorpion venoms could induce diverse physiological responses, including shock, inflammation, arrhythmia, and pain, through their rich content of neurotoxins targeting ion channels (Nav, Cav, Kv). These neurotoxins are potential tools for developing pharmacological treatments for neuropathic pain and other diseases. This study focuses on the venom of *C. exilicauda*, an endemic specie from Baja California, which is characterized for causing intense pain followed by prolonged limb numbness. Therefore, the venom of *C. exilicauda* is being evaluated to identify neurotoxins with modulatory effects on ion channels expressed in dorsal root ganglion neurons. For this project, scorpions of the species *C. exilicauda* were captured and identified in Ensenada, México, to extract venom through electrostimulation. Using patch-clamp electrophysiology, the venom was evaluated on neurons from the dorsal root ganglion neurons of C57 male mice (7-10 days postpartum, n = 4). Ion currents were generated by 0 mV rectangular pulses (100 ms duration) applied every 5 seconds from a voltage holding from -70 mV. Preliminary results indicate that *C. exilicauda* venom reduces both inward by 35.6% (Paired t-test, p = 0.0124, n = 8) and outward by 39% (Paired t-test, p = 0.0328, n = 8) ionic currents and notably inhibits sodium currents modulated by Nav 1.7, suggesting potential to prevent neuron depolarization and action potential generation. Additionally, the effect of total venom was evaluated by patch clamp on HEK293 cells expressing the human Nav1.7 channel, results indicate that *C. exilicauda* venom reduces inward current by 65% (Paired t-test, p = 0.0008, n = 7). Our results suggest the potential to prevent neuron depolarization and action potential generation. This inhibition could have significant implications for treating neuropathic pain. Ongoing work involves detailed analysis in electrophysiology of fractionated venom using High-Performance Liquid Chromatography (HPLC) to identify components with therapeutic potential in pain.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR437.06/B14

Topic: B.03. Ion Channels

Title: Wee1 kinase regulates nav channel function in hipsc-derived cortical neurons

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Abstract: Neurodevelopmental disorders (NDDs) encompass a range of complex conditions, including autism spectrum disorders (ASDs) and schizophrenia (SCZ), characterized by neurological and psychiatric symptoms with limited therapeutic options. Current treatments focus on symptom management rather than addressing the underlying disease progression. Thus, there is a pressing need for drug development targeting disease modification, aiming to prevent, delay the onset, or slow the progression of NDDs. Protein-protein interactions between voltage-gated sodium (Nav) channels and accessory proteins are crucial for neuronal function. Of particular interest is the intracellular fibroblast growth factor 14 (FGF14), an accessory protein that collaborates with kinases to regulate neuronal Nav channel function. Here, we focus on Wee1, a kinase within the AKT and GSK3β signaling pathway, which has shown differential expression in transcriptomic studies of SCZ. Expanding on our previous findings that identified Wee1 as a regulator of FGF14's interaction with Nav1.2 channels, we investigated the impact of genetically silencing Wee1 kinase in human-induced pluripotent stem cell (hIPSC)-derived cortical neurons, utilizing adenoviral constructs AAV-shWee1-GFP and AAV-scramble-GFP. Whole-cell voltage-clamp recordings of sodium currents (INa) were conducted following magneto-transfection of the vectors. Naïve cortical neurons exhibited an average peak INa density of -75.88 ± 6.4 pA/pF (n=6), while cortical neurons expressing AAV-scramble-GFP showed a similar peak INa density of -74.14 ± 7.1 pA/pF (n=7). However, cortical neurons expressing AAV-shWee1-GFP displayed a significant suppression of peak INa density (-27.96 ± 3.4 pA/pF, n=6) compared to AAV-scramble-GFP ($P<0.001$, n=7). Next, we tested the impact of silencing Wee1 on the voltage dependence of activation and steady-state inactivation of INa in cortical neurons. Our findings revealed that AAV-shWee1 expressing cells displayed a significant depolarizing shift in the voltage dependence of activation (-22.56 ± 1.4 mV; $p<0.0001$, n=6) and a hyperpolarizing shift of the steady-state inactivation (-69.75 ± 2.15 mV; $p<0.0001$, n = 7) compared to the AAV-scramble-GFP group. Overall, these results unveil a previously unreported role of Wee1 kinase, which could potentially underlie neuronal endophenotypes associated with SCZ and other NDDs.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

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Topic: B.03. Ion Channels

Support: NIH R01MH124351 (FL)
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Title: Small Molecule Modulation of FGF14/Nav1.6 Protein-Protein Interaction Complex

Authors: *V. JAMES[1], N. DVORAK[2], C. ZHANG[1], Z. HAGHIGHIJOO[1], H. CHEN[3], J. ZHOU[3], F. LAEZZA[4];
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Abstract: Voltage-gated Na+ (Nav) channels play a crucial role in initiating and transmitting action potentials in excitable cells such as neurons. In the central nervous system, Nav1.1, Nav1.2, and Nav1.6 are the main isoforms, each with distinct cellular and subcellular distributions. While the α subunit of Nav channels is responsible for ion conduction, the full functionality of Nav channels relies on interactions with auxiliary proteins at the C-terminal domain of the channels. In previous studies, we demonstrated that the Nav1.6 isoform is the predominant isoform regulated by protein-protein interaction (PPI) with the auxiliary protein fibroblast growth factor 14 (FGF14) in CA1 hippocampal pyramidal neurons and medium spiny neurons of the nucleus accumbens. Furthermore, we previously identified a small molecule,

7605, which specifically targets the PPI interface at the FGF14/Nav1.6 complex. In this study, we have developed second and third-generation derivatives of the original lead compound 7605. We tested over 40 derivatives in quadruplicate at a single concentration (5 µM) to determine their effect on FGF14/Nav1.6 complex formation. This was achieved using a HEK293 double stable cell line expressing CD4-Nav1.6C-tail-NLuc and CLuc-FGF14 via split-luciferase complementation assay (LCA) as the primary assay. Next, we obtained the potency values through a dose-response curve of the compounds, identifying those that inhibited luminescence by at least 50%. Among all the compounds tested via LCA, PW1028 and JY0155 were selected for further dose-response analysis. Their IC50 values were determined to be 247nM and 461nM, respectively. Structure-guided analysis revealed that PW1028 binds to FGF14R117, a critical residue located within a druggable pocket at the FGF14/Nav1.6 PPI interface. Additionally, we found that 1028 modulates depolarizes the voltage-dependence of Nav1.6 channel inactivation by modulating the intramolecular interaction between the inactivation gate and C-terminal domain of the Nav1.6 channel. Ongoing studies aim to compare and contrast the structure and functional activity of PW1028 and JY0155. Overall, these results suggest that modulation of the FGF14/Nav1.6 complex may pave the way for target-selective neurotherapeutics, enabling precise modulation of neuronal excitability for the treatment of a broad spectrum of neuropsychiatric disorders.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

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Title: Unexpected contribution of NaV1.8 to TTX-sensitive action potential conduction in human and rodent vagus nerves

Authors: S. NAIR[1], S. HADLEY[2], M. PATIL[2], ***T. TAYLOR-CLARK**[2];
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Abstract: Voltage-gated sodium channels are essential for action potential (AP) conduction in all nerves, including the vagus. AP conduction in the vagus afferent (80%) and efferent (20%) fibers contributes to the autonomic regulation of visceral organ function. Previous studies have shown that almost all NaV1 pore-forming alpha subunit isoforms are expressed within the vagus

nerve but little is known regarding their contribution to electrical excitability. We performed whole nerve suction recordings of mouse, rat and human vagus nerves to electrophysiologically record axonal AP conduction following distal nerve electrical stimulation. Human vagus nerves were derived from de-identified trachea and lung tissue provided by Lifelink Foundation. Compound action potentials (CAPs) were separated into A- and C-waves and the area under the curve was recorded as a measure of successful conduction of a population of A- and C-fibers, respectively. Our studies in mice and rats show that tetrodotoxin (TTX, 300nM) completely abolished vagal A- and C-wave CAPs indicating that TTX-sensitive NaV1s are essential for all AP conduction. PF-05089771 (mouse NaV1.7 blocker) and ProTX-II (rat NaV1.7 blocker) significantly reduced both the A- (50% reduction) and C-waves (75% reduction) of mouse and rat CAP respectively, suggesting a predominant role for the TTX-sensitive NaV1.7. Inhibitors of the TTX-sensitive NaV1.6 and NaV1.2 isoforms also inhibited vagal CAPs to a limited extent. Despite the fact that vagal CAPs were entirely dependent on TTX-sensitive channels, incubation with A-803467, a selective inhibitor of the TTX-resistant NaV1.8, reduced both the A-and C-wave of the mouse and rat vagal CAP by 50%. Similar observations were noted in human vagus studies: AP conduction was abolished by TTX and inhibited by 60% by the NaV1.8 inhibitor A-803467. Our results show that TTX-sensitive channels (mainly Nav1.7) and TTX-resistant NaV1.8 cooperate in vagal AP conduction such that both are required for most vagal fibers. Pharmacological inhibition of NaV1.8 in the vagus nerve may have profound effects on autonomic regulation of visceral organs.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Title: Modeling Channelopathies in-vitro with iPSC-derived neurons to develop novel therapeutics for pain and epilepsy

Authors: *J. SHIM[1,2], B. S. TANAKA[3], M. A. MIS[4], Y.-C. CHENG[1], L. BARRETT[1], S. D. DIB-HAJJ[5], A. PODURI[6], S. G. WAXMAN[4], C. J. WOOLF[1,2];
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Abstract: Voltage-gated sodium channels expressed in sensory neurons in the peripheral nervous system are critical for transmitting signals from the periphery to the brain, and mutations in sodium channels expressed in nociceptors significantly impact pain sensibility. *SCN9A*, which encodes Nav1.7, is essential for generating action potentials in nociceptors, and gain-of-function mutations in Nav1.7 lead to the pain disorders inherited erythromelalgia and paroxysmal extreme pain disorder, whereas loss-of-function mutations in Nav1.7 cause congenital insensitivity to pain. In the central nervous system, ion channels determine the excitability of neurons, and a growing number of children with neonatal epilepsy are now diagnosed with specific genetic mutations in particular voltage-gated ion channels. For example, *de novo* variants of the gene *KCNQ2*, encoding the Kv7.2 voltage-gated potassium channel, and *SCN8A*, encoding the Nav1.6 voltage-gated sodium channel, are associated with severe early-onset epileptic encephalopathy. Most studies investigating the pathophysiology of voltage-gated ion channel mutations do this by the heterologous overexpression of the human ion channels in non-neuronal cells or rodent neurons, which limits, however, translational implications. We have successfully corrected mutations in the SCN8A, SCN9A, and KCNQ2 genes in iPSCs from patients with IEM or epilepsy and performed GCaMP imaging as well as multi-electrode array (MEA) and patch-clamp recordings in differentiated sensory or cortical neurons to detect pathological excitability and changes after mutation correction. These genetically engineered neuronal models enable us to mimic key features of genetic pain disorders and neonatal epilepsy and provide a powerful tool to investigate the pathophysiological mechanisms of pain and epilepsy. They also enable phenotypic screens for novel therapeutics for channelopathies.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Support: FamilieSCN2A Hodgkin-Huxley award

Title: Unraveling the molecular consequences of SCN2A splice-site genetic variant identified from a child with autism using hiPSC-derived cortical neurons and organoids

Authors: *M. HALURKAR[1], K. WETTSCHURACK[1], M. ROBINSON[1], E. ROSSI[1], H. KADONO[1], M. I. OLIVERO ACOSTA[1], X. CHEN[1], N. M. ATALLAH[1], W. C. SKARNES[2], Y. YANG[1];
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Abstract: *SCN2A* encodes the alpha subunit of the voltage-gated sodium channel $Na_V1.2$, which is essential for proper neuronal function. Mutations in *SCN2A* have been associated with a range of neurodevelopmental disorders, including autism spectrum disorder and epilepsy. In this study, we aimed to investigate a specific splice-site variation (*SCN2A* c.3973-1GtoA) using induced pluripotent stem cells (iPSCs). The c.3973-1GtoA variation was recently identified from a child with autism spectrum disorder (ASD). This variation occurs in the conserved splice site preceding Exon 22. We have used CRISPR/Cas9 editing techniques to engineer the c.3973-1GtoA variation into a reference iPSC cell line, of which a GCaMP6f biosensor was engineered in the AAVS1 safe harbor site of the genome in the iPSCs line. We then differentiated these engineered iPSCs into 2D cortical neurons that are known to express $Na_V1.2$ channels. Using mRNA/cDNA extracted from the differentiated cells, our data suggest that c.3973-1GtoA variation leads to the skipping of Exon 22. Further molecular analysis suggests that the variant causes a shortening of *SCN2A* mRNA across the mutation site but does not alter *SCN2A* mRNA levels upstream or downstream of the mutation. Interestingly, we found that the variation seems to lead to a reduction in $Na_V1.2$ protein expression, suggesting protein degradation. Assessment of various degradation pathways leading to $Na_V1.2$ degradation is ongoing. We are also working on patient-derived iPSCs and 3D cortical organoid models to understand the effects of this variant in advanced systems which may have enhanced physiological relevance. Our results will shed light on the transcriptional and phenotypic changes in neurons by the *SCN2A* c.3973-1GtoA variation, allowing us to identify key disease phenotypes for testing personalized therapeutic interventions.

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Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

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Walther Cancer Foundation
PIDD
PIIN

Title: Unveiling cellular and circuit mechanisms behind autism associated with SCN2A deficiency with both rodent and human cell models

Authors: *J. ZHANG, X. CHEN, M. EATON, B. DEMING, Y. ZHAO, S. KANT, J. WU, Y.-E. YOO, K. WETTSCHURACK, M. HALURKAR, M. I. OLIVERO ACOSTA, Y. YANG; Purdue Univ., West Lafayette, IN

Abstract: Genetic variants in the voltage-gated sodium channel $Na_V1.2$ (encoded by the *SCN2A* gene) are strongly linked with autism spectrum disorder (ASD), epilepsy, as well as other neurodevelopmental disorders. Recent large-scale genetic studies in humans have revealed *SCN2A* carrying loss-of-function (LoF) and protein-truncating mutations as the leading monogenic cause of ASD. Since impairment in social functioning is a major disease hallmark of ASD, thus, it is essential to investigate how *Scn2a* deficiency leads to social deficits. Conventional complete knockout of *Scn2a* in mice is perinatal lethal, while *Scn2a*$^{+/-}$ mice display mild or even a slight increase in social behaviors. We thus developed a viable homozygous mouse model with severe $Na_V1.2$ deficiency by gene-trap strategy. Using this mouse model, we revealed that these mice display major social impairments. As an imbalance between excitation and inhibition (E/I) has been suggested as a common mechanism in ASD, we recorded striatal medium spiny neurons (MSNs) using patch-clamp electrophysiology and found an elevated E/I ratio for the transmissions projected onto these neurons, which contributes to the hyperexcitability observed by *in vivo* Neuropixels recording. Notably, we observed a corrected E/I ratio and rescued social deficits by a global restoration of *Scn2a* expression via adeno-associated virus (PHP.eB-AAV) mediated genetic intervention with flippase (FlpO) in adulthood. Interestingly, while striatum-specific restoration of *Scn2a* expression did not alleviate impaired sociability, restoration of *Scn2a* in the striatum-projecting circuits via retrograde AAV vector alleviated social deficits, indicating the transmissions onto these MSNs play a critical role in the behavioral pathology associated with $Na_V1.2$-deficiency. Using *in vivo* calcium imaging (Inscopix) of freely moving mice as a surrogate to monitor neuronal activity, we perform additional studies to further understand how $Na_V1.2$ deficiency perturbs the neuronal functions and brain circuits resulting in social deficits. Finally, to expand our insights from mice to human, we are investigating the impact of *SCN2A* deficiency on GABA signals using human brain organoid model. Taken together, our study aims to unravel the behavioral and circuit-level phenotypes with the potential reversibility of social impairments in $Na_V1.2$-deficient mice. Furthermore, by unveiling the role of *SCN2A* deficiency in human neurons, we seek to provide a framework for the development of novel interventions to alleviate social deficits related to *SCN2A* deficiency.

Disclosures: J. Zhang: None. **X. Chen:** None. **M. Eaton:** None. **B. Deming:** None. **Y. Zhao:** None. **S. Kant:** None. **J. Wu:** None. **Y. Yoo:** None. **K. Wettschurack:** None. **M. Halurkar:** None. **M.I. Olivero acosta:** None. **Y. Yang:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.12/B19

Topic: B.03. Ion Channels

Support: NIH Grant R01NS117585
NIH Grant R01NS123154
NIH Diversity Supplement

Title: Investigating neural circuits involved in psilocybin's prosocial effects in Scn2a-deficient mice

Authors: *B. DEMING, J. ZHANG, Y. YANG;
Medicinal Chem. and Mol. Pharmacol., Purdue Univ., West Lafayette, IN

Abstract: The CDC estimates that 1 in 36 children in the United States have Autism Spectrum Disorder (ASD). A major characteristic of ASD is social abnormalities. Genetic variants in *SCN2A,* a gene encoding the voltage-gated sodium channel $Na_V1.2$, have been identified as a leading monogenic cause of profound ASD. However, there are few FDA-approved drugs to assist with the social impairments seen in patients with *SCN2A*-related ASD. Recent research on psychedelics, compounds that primarily interact with the serotonergic system, has revealed potential therapeutic benefits in treating multiple psychiatric disorders. Few studies have evaluated the use of psychedelics as potential therapeutics in individuals with ASD, and no study has evaluated their use in *SCN2A*-related ASD. In this study, we examined psilocybin's influence on social deficits seen in *Scn2a*-deficient mice, a mouse model of *SCN2A*-related ASD. Our behavioral analysis revealed that a low dose (0.3 mg/kg) intraperitoneal injection of psilocybin increases the sociability of *Scn2a*-deficient mice during the 3-chamber assay. Recent evidence has highlighted that this compound acts on brain regions such as the Lateral habenula (LHb), a small epithalamic brain region that regulates many social behaviors, and the Dorsal Raphe Nucleus (DRN), the main serotonergic hub of the brain. Additionally, we have found that chemogenetic activation of the LHb and DRN->LHb neurons also increases sociability in *Scn2a*-deficient mice. We are currently investigating the role of the DRN->LHb circuit in psilocybin's prosocial effects. Our results shed light on the importance of neuromodulation in *SCN2A*-related ASD. With recent advocacy to reschedule these compounds, we anticipate that our study will potentially expand the utility of psychedelics as a promising therapeutic to alleviate disease phenotypes related to profound autism, including *SCN2A*-related ASD.

Disclosures: B. Deming: None. **J. Zhang:** None. **Y. Yang:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.13/B20

Topic: B.03. Ion Channels

Support: NIH Grant R01NS117585
NIH Grant R01NS123154
FamilieSCN2A foundation Hodgkin-Huxley Award
PIDD
PIIN

Title: Prime Editing in human iPSCs for generating and correcting SCN2A genetic variations related to epilepsy and autism

Authors: *K. WETTSCHURACK[1], M. ROBINSON[2], W. C. SKARNES[4], Y. YANG[3]; [1]Purdue Univ., Lafayette, IN; [2]Purdue Univ., West Lafayette, IN, ; [3]MCMP, Purdue Univ., West Lafayette, IN; [4]Jackson Lab. of Genomic Med., Farmington, CT

Abstract: Sodium Voltage-Gated Channel Alpha Subunit 2 (SCN2A) is responsible for action potential initiation and propagation in neurons of the central nervous system. Variations in SCN2A, including missense, frame-shift, splicing, and protein-truncating, are known to cause various diseases including autism spectrum disorder (ASD), intellectual disability (ID), and epilepsy. Recent work has demonstrated that SCN2A is one of the leading genes causing monogenic autism and epilepsy. However, there are few effective treatments for SCN2A disorders using current medical interventions. Due to the monogenic nature of these diseases, direct editing of the patient's genome could restore SCN2A functionality and is expected to significantly lessen the symptoms these patients exhibit. DNA editing technology using CRISPR/Cas9 allows for the precise editing of bases. However, it has limited applications for patients because it causes double-stranded breaks in DNA, which may cause unwanted indel formation in the genome. Unlike traditional CRISPR, prime editing (PE) only creates a nick (single-strand DNA break). Thus, PE is considered to have an enhanced safety profile and holds enormous potential for precision genome editing to eventually correct disease-causing genetic variants in patients. We have started our PE effort in human induced pluripotent stem cells (hiPSCs), which have emerged as a preferred system for disease modeling and testing for precision genetic interventions in human genetic background. In iPSCs, we first showed that we could achieve a high editing efficiency in a model iPSCs line where blue fluorescent protein (BFP) was converted to green fluorescent protein (GFP) with a single nucleotide change. After optimizing our conditions in this iPSC line, we showed that we could use our PE system to both create disease-causing SCN2A mutations and convert disease-causing SCN2A mutations to the wild-type sequence. We are currently exploring delivery of the prime editing system to post-mitotic iPSC-derived neurons, potentially allowing for correction in differentiated cells as a potential therapeutic agent.

Disclosures: K. Wettschurack: None. **M. Robinson:** None. **W.C. Skarnes:** None. **Y. Yang:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.14/B21

Topic: B.03. Ion Channels

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FamilieSCN2A foundation the Action Potential Grant
FamilieSCN2A foundation Hodgkin-Huxley Award

Title: Unraveling molecular and cellular alterations caused by Scn2a deficiency through single-nucleus transcriptomic analysis

Authors: *Y.-E. YOO, P. MANDAL, J. ZHANG, X. CHEN, M. EATON, Y. YANG;
Purdue Univ., West Lafayette, IN

Abstract: SCN2A gene, encoding a voltage-gated sodium channel $Na_v1.2$, is crucial for action potential initiation and propagation. The loss-of-function mutations in the SCN2A gene have been linked to neurodevelopmental disorders such as autism spectrum disorder and epilepsy. Our lab has established a *Scn2a*-deficient mouse model, which displays severe neuronal and behavioral deficits. However, the cellular and molecular mechanisms underlying these phenotypes at a single-cell resolution remain elusive. In this study, we utilized single nucleus RNA sequencing (snRNA-seq) to investigate the medial prefrontal cortex (mPFC) of wild-type (WT) and homozygous *Scn2a*-deficient (HOM) mice. Our analysis unexpectedly uncovered altered cell type proportions within the mPFC between WT and HOM groups. We noticed more inhibitory neuron clusters in HOM mice than in our WT mice. Ongoing analysis will confirm the inhibitory neuron type through immunostaining in the mPFC region. Furthermore, ingenuity pathway analysis (IPA) revealed that differentially expressed genes (DEGs) in inhibitory neuron types were enriched in glutaminergic receptor signaling pathway, including pathways related to synaptogenesis signaling and synaptic long-term depression. All these findings will reveal the impact of *Scn2a*-deficiency on the composition of different cell populations and gene expression profile. Together, these insights may advance our understanding of the underlying pathology and pave the way for targeted therapeutic strategies directed at novel molecular targets in a cell-type-specific manner.

Disclosures: Y. Yoo: None. **P. Mandal:** None. **J. Zhang:** None. **X. Chen:** None. **M. Eaton:** None. **Y. Yang:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.15/B22

Topic: B.03. Ion Channels

Support: Showalter Research Trust

Title: Dissecting the mechanisms of seizure phenotypes in scn2a-deficient mice using neuropixels and two-photon imaging

Authors: *Y. ZHAO;
Purdue Univ., West Lafayette, IN

Abstract: Mutations in the *SCN2A* gene, which encodes the NaV1.2 sodium channel, are linked to severe neurological disorders, including epilepsy, autism spectrum disorder, or intellectual disability (ASD/ID). The SCN2A loss-of-function (LoF) mutations particularly result in ASD/ID and late-onset epileptic encephalopathy. This study aims to elucidate the underlying mechanisms associated with epilepsy linked to SCN2A deficiency using high-resolution Neuropixels recording and two-photon calcium imaging in a Scn2a-deficient mouse model. We used PTZ (pentylenetetrazole)to induce seizures in these *Scn2a*-deficient mice. We are studying neural activity during baseline and PTZ-induced seizure states by recording with Neuropixels, which will provide comprehensive, multi-region electrophysiological data longitudinally across the brain. Notably, we are observing elevated synchronization patterns, which are strongly enhanced across multiple brain regions during induced seizure episodes in *Scn2a*-deficient mice. Conversely, two-photon imaging was conducted in motor cortical layers to visualize calcium transients reflective of neuronal activity at the cellular level and hypersynchronizations at the network level. Furthermore, we are performing experiments to test the efficacy of the available sodium channel blockers like phenytoin and GABA enhancing anti-epileptic medication (e.g., clonazepam) on these identified neuronal and circuitry phenotypes. This study will highlight the utility of high-throughput Neuropixels recording and advanced neuroimaging techniques to uncover the complex neural basis of epilepsy associated with *SCN2A* deficiency. Our study would also provide basis for evaluating the effectiveness of potential therapeutic interventions.

Disclosures: Y. Zhao: None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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Topic: B.03. Ion Channels

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FamilieSCN2A foundation for the Action Potential Grant
FamilieSCN2A Foundation Hodgkin-Huxley Award
NIH Grant R01NS117585
NIH Grant R01NS123154

Title: Functional assays of induced pluripotent stem cell derived 2D cortical neurons and 3D cortical organoids carrying SCN2A splice-site genetic variant identified in a child with autism

Authors: *M. ROBINSON[1], M. HALURKAR[2], K. WETTSCHURACK[2], J. ZHANG[2], Y.-E. YOO[2], M. I. OLIVERO ACOSTA[2], B. D. ZIRKLE[2], X. CHEN[2], E. ROSSI[2], C. YUAN[1], W. C. SKARNES[3], Y. YANG[2];
[1]Chem. Engin., Purdue Univ., West Lafayette, IN; [2]MCMP, Purdue Univ., West Lafayette, IN; [3]Jackson Lab., Farmington, CT

Abstract: The voltage-gated sodium channel Nav1.2 is encoded by the *SCN2A* gene and is essential for the proper function of principal neurons in the brain including excitatory neurons of the cortex and hippocampus. SCN2A mutations are the leading monogenic cause of autism spectrum disorder (ASD) and are also known to cause epilepsy. In this electrophysiology study, we investigate the effects of a specific splice-site variant (SCN2A c.3973-1G>A) in engineered induced pluripotent stem cells (iPSCs) in the Kolf2.1J reference line as well as patient-derived line together with isogenic controls. The c.3973-1G>A mutation variant was recently identified in a child with ASD. The mutation site occurs in a conserved splice site immediately preceding exon-22, which spans one transmembrane domain and partial region of the Na^+ pore-forming domains. We utilized a genetically engineered Kolf2.1J reference line containing a GCaMP6 biosensor within the AAVS1 safe harbor site to introduce the splice-site variant by CRISPR/CAS9. We then differentiated these engineered iPSCs into 2D cortical neurons that are known to express Nav1.2 for calcium imaging, multielectrode array and patch clamp recording. Next, we produced 3D cortical organoids for 3brain high-density MEA high resolution electrophysiology recording. These experiments allow us to test the hypothesis that this splice-site mutation (c.3973-1G>A) results in decreased electrophysiological activity, reduced network bursting and dysfunctional Ca2+ signaling. Next, we used genome-editing to correct the patient mutation generating an isogenic iPSC line and are repeating key experiments to validate our findings obtained in engineered iPSCs. Our results will shed light on the functional consequences of the *SCN2A* splice-site variant on neuronal electrophysiological properties, including Ca^{2+} signaling, action potential and neuronal signal propagation, allowing us to identify key disease phenotypes for testing personalized therapeutic interventions.

Disclosures: M. Robinson: None. **M. Halurkar:** None. **K. Wettschurack:** None. **J. Zhang:** None. **Y. Yoo:** None. **M.I. Olivero acosta:** None. **B.D. Zirkle:** None. **X. Chen:** None. **E. Rossi:** None. **C. Yuan:** None. **W.C. Skarnes:** None. **Y. Yang:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.17/B24

Topic: B.03. Ion Channels

Support: NIH HEAL grant: U19NS126038
VA RRD Center grant: RX002999

Title: Rendering Nav1.7 channels permeable to potassium ions creates an electrical shunt and reduces DRG neuronal excitability

Authors: *M. ESTACION[1,2], X. CHENG[3,2], F. DIB-HAJJ[4,2], J. DIAZ QUIROZ[5], T. J. PRICE[6], G. O. DUSSOR[7], E. EISENBERG[8], S. G. WAXMAN[1,2], J. ROSENTHAL[9], S. D. DIB-HAJJ[10]; [1]Neurol., Yale Univ., New Haven, CT; [2]VAMC, West Haven, CT; [3]Neurol., Yale Med. Sch., West Haven, CT; [4]Yale Univ., New Haven, CT; [5]Marine Biol. Lab., Woods Hole, MA; [6]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas Neurosci. Undergraduate Program, Richardson, TX; [7]Neurosci., Univ. of Texas at Dallas, Richardson, TX; [8]Tel Aviv Univ., Tel Aviv, TX; [9]Eugene Bell Ctr., Marine Biol. Lab. (MBL), Woods Hole, MA; [10]Dept Neurol, Yale Sch. of Med. and VAMC, West Haven, CT

Abstract: The Na^+/K^+ selectivity of eukaryotic voltage-gated sodium (Nav) channels is determined by the selectivity filter (SF) which is composed of four highly conserved residues Asp (D), Glu (E), Lys (K) and Ala (A), also referred to as the DEKA motif, one from each of the external side of the four pore modules (PM1-4). K1395 (Nav1.7 numbering) in this motif is the most critical determinant for the Na^+ selectivity; substitutions of this residue abolish the Na^+ selectivity, conferring higher permeability to K^+ and in some cases Ca2+, on the mutant channel. The rationale for this study is that a Nav1.7 channel with a high permeability to K^+ can act as an electrical shunt to reduce the strength of action potentials and attenuate neuronal firing, and that channels modified in this manner could be used in a therapeutic setting. Altering Nav1.7 ion selectivity by editing the 1395 codon (AAG) can be achieved using site-directed RNA editing, a molecular system which generates programmed A-to-I RNA edits of the second adenosine where I is a translational mimic for guanosine can recode K1395 to R (AGG). K1395R substitution is expected to make the channel permeable to K^+ but not Ca^{2+}. However, selective editing of the first adenosine (AAG to GAG) or both adenosines (AAG to GGG) generates E or G and either would make the channel permeable to Ca^{2+} as well. We generated Nav1.7 channels with three substitutions at codon 1395 (K1395R, E, or G) and confirmed the effects of these substitutions on the channel's ion selectivity, biophysical and pharmacological properties. We also examined the effect of the expression of K1395R channels on DRG neuronal firing. Voltage-clamp recordings in HEK293 cells show that K1395R is equally permeable to Na^+ and K^+, but not to Ca^{2+}; it becomes TTX-R but retains sensitivity to Nav1.7-selective blocker ProTxII. Unlike K1395R, both K1395E and K1395G channels are also permeable to Ca^{2+}, TTX-R but ProTxII sensitive. Coexpression of Nav1.7-WT and Nav1.7-K1395R channels results in a mixed current with a mean reversal potential that falls between +60mV and 0mV with the shift of mixed reversal potential correlating with the relative proportions of Nav1.7-WT and Nav1.7-K1395R channels. Thus, we can use this approach to estimate the efficiency of mRNA editing in HEK293 cells by observing the mixed reversal potential. The expression of Nav1.7-K1395R in DRG neurons results in a reduction of peak AP amplitude, an increase in threshold to first spike, and significant reduction in repetitive firing. Thus, targeted mRNA editing of Nav1.7 channels to make them permeable to K^+ but not Ca^{2+} represents a novel approach to modulating sensory neuron excitability as a potential analgesic.

Disclosures: M. Estacion: None. **X. Cheng:** None. **F. Dib-Hajj:** None. **J. Diaz Quiroz:** None. **T.J. Price:** None. **G.O. Dussor:** None. **E. Eisenberg:** None. **S.G. Waxman:** None. **J. Rosenthal:** None. **S.D. Dib-Hajj:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.18/B25

Topic: B.03. Ion Channels

Support: NIH HEAL grant U19NS126038
VA RRD Center grant RX002999

Title: Site-directed RNA editing of the Nav1.7 selectivity filter to increase permeability to potassium ions

Authors: *X. CHENG[1,2], M. R. ESTACION[1,2], J. F. DIAZ QUIROZ[3], F. DIB-HAJJ[1,2], S. TYAGI[1,2], D. SIPOLSKI[3], L. SISKEL[3], T. J. PRICE[4], G. O. DUSSOR[5], E. EISENBERG[6], S. G. WAXMAN[1,2], J. ROSENTHAL[3], S. D. DIB-HAJJ[1,2];
[1]Yale Med. Sch., New Haven, CT; [2]Center for Rehabilitation Research, VA Connecticut Healthcare System, West Haven, CT; [3]Eugene Bell Ctr., The Marine Biol. Lab., Woods Hole, MA; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas Neurosci. Undergraduate Program, Richardson, TX; [5]Neurosci., Univ. of Texas at Dallas, Richardson, TX; [6]Tel-Aviv Univ., Tel Aviv, Israel

Abstract: Voltage-gated sodium channel Nav1.7 has been a broadly studied target for analgesic development focused mostly on small molecule inhibitors. A novel approach, expected to mute Nav1.7 function, is to make the channel permeable to K^+, enabling it to act as an electrical shunt to attenuate firing of nociceptors. Site-Directed RNA Editing (SDRE) is a system that generates the conversion of precisely selected adenosines to inosine (A-to-I) mediated by engineered or native adenosine deaminases acting on RNA (ADARs), and a guide RNA (gRNA). Inosine is a translational mimic for guanosine, and therefore A-to-I edits can recode amino acids. The ion selectivity filter of Nav channels resides in the external pore and consists of the DEKA motif, one residue from each of the four channel domains. The lysine residue from domain III (K1395 in hNav1.7), encoded by AAG, is critical for ion selectivity and can be edited to generate R (AGG), G (GGG), or E (GAG). The edited channels become highly permeable to K^+, but only K1395R retains the WT selectivity against Ca^{2+}. Using *in vitro* and *in cellula* assays, optimized gRNAs were generated using a SELEX-like approach. The editing enzyme λNDD carries a dsRNA recognition motif from the λ bacteriophage and the deaminase domain of human ADAR2. Using an automated patch-clamp system (Sophion Qube 384) and an HEK293-hNav1.7 (WT) stable cell line adapted to grow in suspension, we developed a high-throughput assay for evaluating editing efficacy and selectivity of SDRE reagents based on reversal potential (V_{rev}) and K^+ permeability. Suspension cultures of WT cells were transfected with constructs

containing 4 copies of gRNA and a copy of λNDD in a P2A-eGFP vector. Transfected cells were sorted based on intensity of green fluorescence and loaded on a Qchip together with untransfected WT and HEK293-h1.7s-K1395R cells as controls. Voltage-gated Na^+ and K^+ currents were recorded by a series of step depolarizations in NaCl and KCl external bath solutions. The V_{rev} (V_{Na} and V_K) was determined by Boltzmann IV fit, and the relative permeability to K^+ (P_K/P_{Na}) was calculated based on the shift of V_{rev} (V_{Na} - V_K; liquid junction potentials were corrected). Editing efficacy in each cell (reflected as percentage of edited channels) was determined based on the relative K^+ permeability of recorded currents using a function derived from the Goldman-Hodgkin-Katz equation. Our data demonstrate a reproducible functional editing efficiency >30% using an active SDRE and no editing with an inactive SDRE (scrambled gRNA/λNDD), demonstrating that this new assay can reliably determine and evaluate the efficacy of hNav1.7 channels by optimized SDRE reagents.

Disclosures: X. Cheng: None. **M.R. Estacion:** None. **J.F. Diaz Quiroz:** None. **F. Dib-Hajj:** None. **S. Tyagi:** None. **D. Sipolski:** None. **L. Siskel:** None. **T.J. Price:** None. **G.O. Dussor:** None. **E. Eisenberg:** None. **S.G. Waxman:** None. **J. Rosenthal:** None. **S.D. Dib-Hajj:** None.

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.19/B26

Topic: B.08. Epilepsy

Title: A functional phenotypic in vitro model of Dravet Syndrome with an SCN1A loss of function induced with an AAV shRNA construct

Authors: O. H. SCHROEDER[1], L. SCHULTZ[1], M. WINKLER[1], A.-M. KNOSPE[1], *K. JÜGELT[1], M. PETERS[2];
[1]NeuroProof Systems GmbH, Rostock, Germany; [2]Translational Sci., Longboard Pharmaceuticals, La Jolla, CA

Abstract: Mutations in brain voltage-gated sodium channel NaV1.1 (SCN1A) have been associated with Dravet Syndrome - a catastrophic form of epilepsy or other forms of epilepsy and other diseases such as genetic epilepsy - febrile seizures plus (GEFS+), Doose syndrome, West syndrome, Lennox-Gastaut syndrome, Rett syndrome, and nonsyndromic epileptic encephalopathy, as well as non-epileptic diseases such as hemiplegia migraine and autism spectrum disorder (ASD).
(SCN1A) loss-of-function variants cause the severe epilepsy Dravet syndrome, as well as milder phenotypes associated with genetic epilepsy with febrile seizures plus. We therefore reasoned that a general knockdown of it can present a relevant phenotypic model of such mutations.
Loss of SCN1A causes selective deletion of NaV1.1 channels located at GABA-ergic inter-neurons, and its knockdown causes a hyperexcitation in electrophysiological activity.
We used an AAV shRNA construct to knock down expression of SCN1A in cultures of mouse

frontal cortex. Following optimization of knockdown conditions, we cultivated the neurons on 48 well MEA plates, and recorded network activity after 28 div. Scn1a knockdown cultures showed significant hyperexcitation when compared to control groups.Norfenfluramine at 10 µM reduced hyper-exitation of frontal cortex cultures..
Thus, we could demonstrate that AAV shRNA downregulation of SCN1A gene is a reliable and effective model of Dravet Syndrome. Our model can be used in drug screening and further research on this disease.

Disclosures: O.H. Schroeder: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof Systems GmbH. **L. Schultz:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **M. Winkler:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **A. Knospe:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **K. Jügelt:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **M. Peters:** A. Employment/Salary (full or part-time):; Longboard Pharmaceuticals, Inc..

Poster

PSTR437: Voltage-Gated Sodium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR437.20/B27

Topic: B.08. Epilepsy

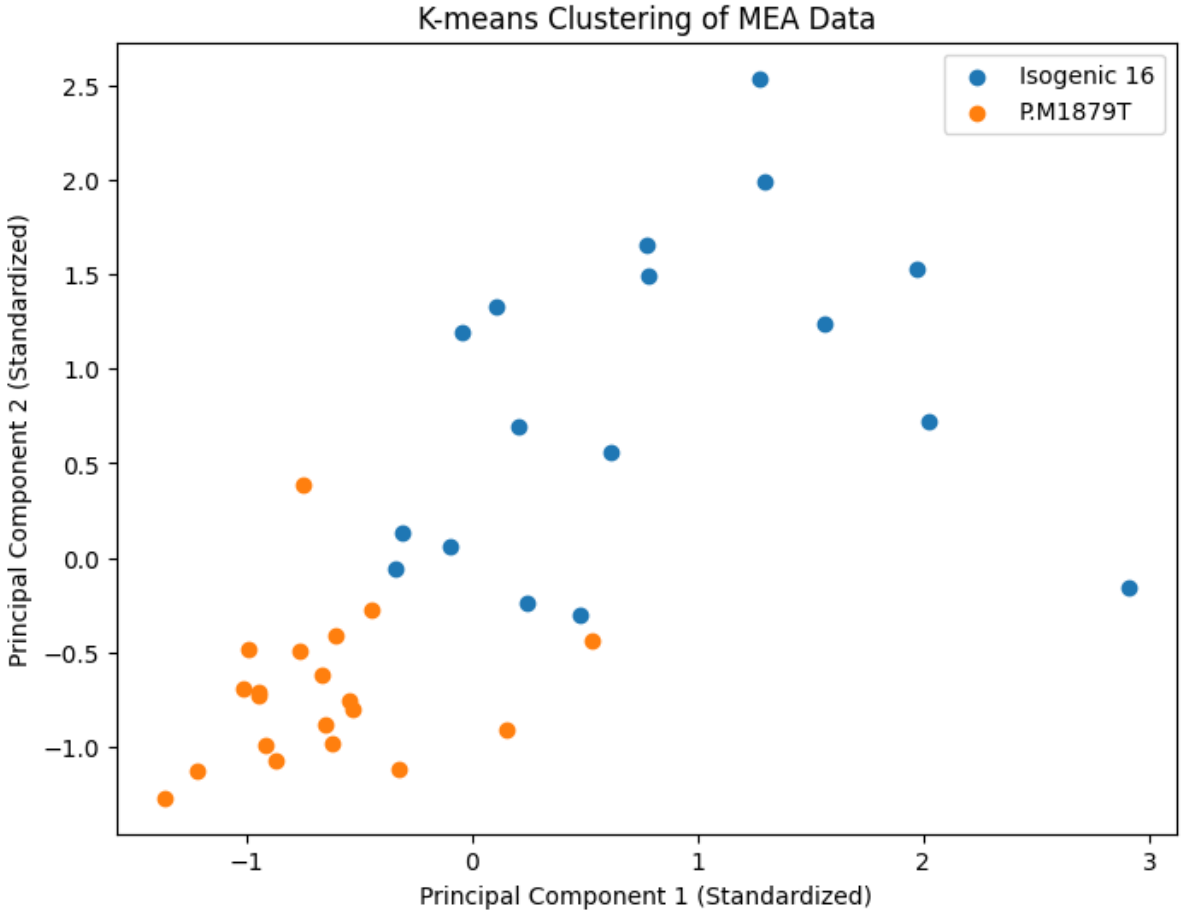
Support: NIH Grant K08NS121601
NIH Grant U54NS108874

Title: Conventional and novel approaches to analyze functional impact of a SCN2A-related excitatory neuronopathy

Authors: S. PANDA[1], E. EASTWOOD[1], A. L. GEORGE[2], *S. ADNEY[3];
[1]Neurol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Pharmacol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [3]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Mutations in the SCN2A gene cause a spectrum of disease severity, from self-limited early infantile seizures to early-onset epileptic encephalopathy. Studies of SCN2A variant function have rapidly accelerated in the past several years, yet few studies assess the functional impact in human neurons. Here we analyze the impact of excitatory neurons in patient-derived iPSCs from a patient with early-onset epilepsy using a combination of conventional and novel techniques.
Induced pluripotent stem cells (iPSCs) were reprogrammed from a patient with early-onset epilepsy containing the p.M1879T variant. Channels with this variant have altered fast inactivation, predicted to result in gain-of-function. To understand the impact of these mutations on human neurons, we employed lentivirus-directed differentiation to generate excitatory

neurons, comparing the patient line with an isogenic control generated with CRISPR-Cas9. We then analyzed intrinsic excitability with whole-cell patch clamp. Compared to the isogenic control, the patient line exhibited significantly increased evoked firing frequencies at higher current injection. To assess population firing properties, we cultured neurons on 48-well multi-electrode arrays (MEAs). We used principal component analysis to perform unsupervised clustering, which showed time-resolved separation of the two genotypes. A random forest regression model was used to extract significant features of the MEA recordings.
To evaluate spontaneous activity with single neuron resolution, we employed the voltage reporter ASAP3 delivered via lentivirus. We compared the spontaneous firing properties and synchronicity of the SCN2A variant and isogenic control, as well as their response to perfusion of chemicals like GABA and the pro-convulsant drug 4-AP.
In this work we employed conventional and novel methods to analyze the functional impact of a SCN2A variant implicated in early-onset epilepsy. Importantly, our methodology can be extended towards assessment of iPSC-derived neurons in a variety of genetic diseases.



Disclosures: S. Panda: None. **E. Eastwood:** None. **A.L. George:** None. **S. Adney:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

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Title: Early Dyshomeostatic Compensation Leads to Synaptic Dysfunction in KCNQ2 Developmental and Epileptic Encephalopathy in Patient-Specific iPSC-Derived Neurons

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Abstract: Heterozygous loss-of-function mutations in *KCNQ2* are associated with Developmental and Epileptic Encephalopathy (DEE), which presents with neonatal seizures and a spectrum of cognitive, developmental, and motor deficits. Despite seizure remission, DEE patients continue to face lifelong intellectual and developmental disabilities with no treatment options. Using induced pluripotent stem cells (iPSCs) and CRISPR/Cas9 gene editing, we established a KCNQ2-DEE disease model system and previously demonstrated that neurons derived from a single KCNQ2-DEE patient carrying a R581Q pathogenic variant exhibited early onset of spontaneous activity and enhanced burst-suppression-like firing relative to their isogenic mutation-corrected controls, as measured by multi-electrode array (MEA) recordings (PMID 33544076). Here, we extend the broader relevance of these findings by application of multivariable machine learning algorithms on MEA datasets and identification of common firing features across additional DEE patient iPSC lines, carrying different *KCNQ2* mutations (R207W, H228R, T274M, P335L). Concurrent gene expression studies indicated a consistent upregulation of Ca^{2+}-activated (SK) K^+ channels across all DEE lines, associated with faster action potential repolarization and larger post-burst afterhyperpolarizations over several weeks in culture. Furthermore, we examined the long-term consequences of these maladaptive changes on synaptic and network function by assessing the reliability of evoked responses on MEAs and through immunostaining of synaptic densities in iPSC-derived neurons from DEE patients. We found that as neurons began to form synaptic connections and participate in synchronous network bursts, DEE patient neurons exhibited decreased responsiveness to electrical stimulation compared to their respective isogenic controls. This differential response was abrogated by treatment with synaptic blockers, suggesting a reliance on synaptic dysfunction rather than altered intrinsic excitability. Immunostaining further confirmed reduced synaptic puncta density in DEE neurons. Notably, these reduced evoked responses are phenocopied in control neurons by chronic M-channel inhibition with XE991 and rescued in patient neurons with chronic Kv7 activator (retigabine) treatment. Our findings elucidate the role of synaptic dysfunction in KCNQ2-DEE and offer critical insights into the complex interplay of mechanisms that govern

both short- and long-term homeostatic plasticity during neurodevelopment, thereby enhancing our understanding of a genetic disease beyond the immediate effects of the mutation itself.

Disclosures: D. Simkin: None. **S.M.A. Wafa:** None. **M. Gharib:** None. **M. Forrest:** None. **K.A. Marshall:** None. **P. Penzes:** None. **A.L. George, Jr:** None. **E. Kiskinis:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.02/B29

Topic: B.03. Ion Channels

Support: DA000552

Title: Differential transcriptional consequences of the potassium channel agonists, flupirtine, chlorzoxazone, and diazoxide, in the rat nucleus accumbens

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Abstract: Ion channels are integral transmembrane proteins that selectively control the influx and efflux of important physiological ions such as Na+, K+, Ca2+, and Cl− into and from cells or intracellular organelles. They control cytoplasmic and intraorganellar ionic concentrations while regulating membrane potential and cellular homeostasis. Of interest, potassium channels regulate action potential propagation and neurotransmission in the brain. Recent experiments in our laboratory have indicated that potassium channels might be important in the control of methamphetamine self-administration by rats. As part of our efforts to understand the impact of the activation of these channels, we conducted the present study that aimed at measuring the transcriptional consequences of three, clinically approved, potassium channel agonists in the nucleus accumbens of male Sprague-Dawley rats. Specifically, we used flupirtine, a KCNQ/Kv7 agonist; chlorzoxazone, a KCNMA1/Kca1.1/BKalpha agonist; and diazoxide, an agonist at KCNJ1/Kir1.1/ROMK, KCNJ5/Kir3.4/Girk4/KATP1, KCNJ8/Kir6.1/uKATP1, and KCNJ11/Kir6.2/iKATP channels. A single injection of either flupirtine (1 or 10 mg/kg) (FLU1, FLU10), diazoxide (5 or 10 mg/kg) (DIA5, DIA10), chlorzoxazone (5 or 10 mg/kg) (CHL5, CHL10), or of the vehicle (Veh) was administered to rats. Animals were euthanized at 2 hours after the injections and their nucleus accumbens was dissected for the measurements of mRNA expression. Quantitative RT-PCR analysis revealed increased expression of the voltage-gated channel *Kcna1* after FLU10, DIA10, and CHL10 injections in comparison to the Veh groups. In addition, rats treated with DIA5, CHL5, and CHL10 doses experienced decreased *Kcna3* mRNA expression in comparison to Veh animals. In contrast, *Kcna5* mRNA levels were increased in DIA10 rats compared to DIA5 rats. There were no significant drug-induced changes in the

expression of calcium /sodium- activated channels including *Kcnma1*, *Kcnmb2*, and *Kcnn1*. Taken together, these observations indicate that administration of potassium channel activators can have significant transcriptional consequences in the NAc, a brain region known to be important to reward mechanisms. Future studies will need to investigate their genome-wide transcriptional consequences in various brain regions. In any case, our present observations support the idea of testing potential beneficial effects of these agents, which are presently being clinically used in neurological disorders, in the treatment of substance use disorders (SUD).
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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.03/B30

Topic: B.03. Ion Channels

Support: NIH R01 MH131317
NIH T32 DA018926-18S1

Title: Oxytocin modulates dentate granule cell excitability via K_V1

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Abstract: Social memory, the ability to recognize, maintain, and update information about others, is critical to navigating our environment. Evidence demonstrated that the hippocampus, and area CA2 in particular, plays a pivotal role in social memory. The neuropeptide oxytocin, traditionally recognized for its roles in lactation, water retention, and childbirth, is important to hippocampal social memory functions as knockout of the oxytocin receptor in area CA2 impaired social memory in mice. Oxytocin increases CA2 pyramidal neuron excitability by inhibiting M-current potassium channels. In addition to area CA2, there is some data to suggest that the dentate gyrus also plays a role in social memory. Oxytocin receptors are expressed in the granule cell layer of the dentate gyrus and knockout of the oxytocin receptor in anterior hilar neurons of the dentate gyrus impairs social recognition in mice. Given the potential role of the dentate gyrus in social memory, it is crucial to investigate oxytocin signaling in the dentate gyrus. We performed whole-cell current clamp recordings on dentate granule cells and tested the effect of the oxytocin agonist Thy^4, Gly^7-oxytocin (TGOT) on neuronal excitability. We found that bath application of 0.4 µM TGOT increases action potential firing in response to depolarizing current injections. Application of TGOT did not significantly change dentate

granule cell input resistance but did hyperpolarize the threshold for action potential generation. Previous research demonstrated that K_V1 voltage-gated K^+ channels influence action potential threshold in dentate granule cells. We found that block of K_V1 channels, with 50 µM 4-aminopyridine, occludes the effects of oxytocin on action potential threshold suggesting that K_V1 channels may be modulated by oxytocin. Fragile X Syndrome is highly heritable and characterized by cognitive and behavioral deficits such as social withdrawal, phobia, and avoidance. Fmr1 knock-out (FX) mice, a model of Fragile X syndrome, display increased social anxiety and decreased social novelty recognition. We found that the action potential threshold was depolarized in dentate granule cells from FX mice compared to wild-type mice. Furthermore, we found that the magnitude of the effect of TGOT on action potential threshold may be smaller in FX dentate granule cells. These results suggest that oxytocin regulates dentate granule cell excitability in part by downregulation of K_V1 channels. Additionally, deficits in social memory in Fragile X syndrome may be due in part to reduced dentate granule cell excitability and impaired oxytocinergic modulation of AP threshold.

Disclosures: A. Marron: None. **D.H. Brager:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR438.04/B31

Topic: B.03. Ion Channels

Support: NIH Grant NS102239

Title: Neuronal potassium channel activity triggers initiation of mRNA translation through binding of translation regulators

Authors: *J. WU[1], T. J. MALONE[2], Y. ZHANG[3], R. CHEN[4], P. LICZNERSKI[5], E. A. JONAS[6], L. K. KACZMAREK[7];
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Abstract: Neuronal activity stimulates the translation of mRNAs in neurons, a process required for normal learning and development. Although translation is regulated by cytoplasmic factors such as the RNA-binding protein FMRP (Fragile X Mental Retardation Protein), whose absence causes Fragile X Syndrome, and its binding protein CYFIP1 (Cytoplasmic FMR1 Interacting Protein 1), the exact mechanism that links translation to neuronal activity is not understood. We have found that translation is stimulated when FMRP and CYFIP1 translocate to the plasma membrane potassium channel Slack (KCNT1, $K_{Na}1.1$). When the channels are activated, this releases both factors from eIF4E (Eukaryotic Initiation Factor 4E), where they normally inhibit

initiation of translation. A constitutively active Slack mutation (*Slack-R455H*), as well as pharmacological stimulation of the wild-type channel, increases binding of FMRP and CYFIP1 to the channel, enhancing the translation of a reporter for β-actin mRNA in cell lines and increasing the synthesis of β-actin in the dendrites of cortical neurons. The effects of Slack mutations on activity-dependent translation may explain the very severe intellectual disability produced by these mutations in humans. Our ongoing experiments explore whether suppressing the Slack channel attenuates the activity-dependent translation induced by its mutations. Antisense oligonucleotides (ASOs), modulating gene expression and mRNA splicing, show promise for treating neurological diseases. We have determined that a specific ASO targeting the core domain of the Slack channel suppresses its expression and normalizes potassium and sodium currents in the *Slack-R455H* mutant neurons. Our findings suggest that Slack channel suppression releases FMRP and CYFIP1 from the *Slack-R455H* mutant channel to eIF4E, attenuating activity-dependent synthesis of proteins such as $Na_V1.6$, whose mRNAs are targets of FMRP. Our findings on the coupling of neuronal activity to translational regulation may provide a new avenue for understanding and treating Fragile X syndrome and other neurological disorders.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

Support: NIH grant DC01919 to LKK

Title: Binding of the Kv3.4 potassium channel to the cell adhesion molecule PCDH9 triggers neurite outgrowth

Authors: *Y. ZHANG[1], N. J. DELUCA, III[2], J. WU[3], W. LAM[4], S. KUMAR[5], M. MARABITA[6], A. BIOSA[7], N. PILATI[8], M. GUNTHORPE[9], T. D. ALEXANDER[10], C. H. LARGE[11], M. BHATTACHARYYA[3], M. L. COVARRUBIAS[12], L. SONG[4], L. K. KACZMAREK[1];
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Abstract: Kv3.4 is a voltage-dependent potassium channel that undergoes rapid activation and inactivation on depolarization. It has been found to play a role in neuronal outgrowth during development, but its mode of action is not clear. We carried out a Yeast-Two Hybridization screen using the cytoplasmic Kv3.4 C-terminus as bait, and found that protocadherin 9 (PCDH9), a calcium-dependent cell adhesion molecule, is a major Kv3.4-binding protein. PCDH9 readily coimmunoprecipitates with Kv3.4 from brain extracts but does not bind Kv3.1 or K3.3, two closely related channels. Functional Kv3.4 channels absolutely require this interaction with PCDH9, such that Kv3.4 protein and currents are abolished by PCDH9 knockout in Kv3.4 expressing cells, as well as in cerebellar granule neurons. PCDH9 contains a WIRS (Wave Regulatory complex Interacting Sequence) that links it to the WAVE actin-nucleating complex. To test the effects of Kv3.4 on actin nucleation, we expressed Kv3.4 into CHO cells and then stained with phalloidin to visualize actin filaments. We found that Kv3.4 potently stimulates the outgrowth of filopodia, and this effect is reversed by knockout of PCDH9 or by overexpression of the PCDH9-specific WIRS sequence peptide that blocks the interaction of PCDH9 with the WAVE complex. The formation of filopodia does not require K^+ flux through Kv3.4 itself but requires a physiological membrane potential (~-60 mV). Thus, a Kv3.4 pore mutation that does not conduct K^+ ions apparently fails to trigger F-actin extension when expressed alone in CHO cells, which have a resting potential of ~-20 mV. When, however, the Kv3.4 pore mutant is co-expressed with another channel (Kv3.1) that has no effect on actin nucleation but brings the membrane potential to -60 mV, the effect of the pore mutant on filopodial extension is identical to that of wild type Kv3.4, suggesting that voltage-dependent inactivation of Kv3.4 blocks its actions on PCDH9. To extend these findings to neurons, we generated the $Kv3.4^{-/-}$ mice using Crispr Cas9 gene editing. These have motor deficits with multiple abnormalities in neuronal migration and development in the cerebellum. Cerebellar ganglion neurons cultured from $Kv3.4^{-/-}$ mice have greatly reduced neurite outgrowth and branching, an effect that is mimicked by introducing the PCDH9-WIRS peptide into wild type neurons. Overexpression of the Kv3.4 pore mutate construct into the $Kv3.4^{-/-}$ rescued the stunted neurite outgrowth. Our findings suggesting that gating of the Kv3.4 channel directly activates the interaction of PCDH9 with the WAVE complex, and that this interaction is required for normal neuronal development.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.06/B33

Topic: B.03. Ion Channels

Support: NS102239
DC01919

Title: Slack (KCNT1) potassium channels regulate the structure of the inner mitochondrial membrane in neurons

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Abstract: The Slack channel (KCNT1, KNa1.1) is a tetrameric, sodium-activated potassium channel expressed in neurons of the cerebral cortex, as well as in multiple other brain regions. Human Gain-of-function mutations in *Slack* channels result in several forms of childhood epilepsy and severe intellectual disability. Mice lacking Slack channels have been shown to be deficient in long-term potentiation and long-term depression of synaptic connections in response to neuronal stimulation. The cytoplasmic C-terminal of Slack interacts with regulators of mRNA translation and the activation of Slack channels triggers translation of a subset of neuronal proteins. Proteomic analysis of the cerebral cortex of *Slack* knockout mice and of mice bearing the gain-of-function *Slack-R455H* mutation has revealed that loss of Slack results in changes in expression of a wide variety of neuronal proteins. Most significantly upregulated in the brain of *Slack*$^{-/-}$ mice are many proteins resident in the inner mitochondrial membrane, components of complexes III, IV and V. We have now confirmed several of these by immunoblotting. In addition, we have carried out an analysis of mitochondrial structure in cortical neurons by electron microscopy. We have found that the density of mitochondrial cristae is very significantly increased in *Slack-/-* mice. Moreover, in mitochondria from wild-type animals, the number of cristae and their packing density varies over a wide range. In contrast, in the *Slack*$^{-/-}$ neurons, the packing of cristae is significantly more uniform, with a very reduced standard deviation in cristae density. In addition to the cerebral cortex, we analyzed both presynaptic and postsynaptic mitochondria at the calyx of Held synapse in the auditory brainstem, a synapse that a very high metabolic demand and normally fires at may hundreds of hertz. We found that, as in cortex, cristae density was greatly elevated in *Slack*$^{-/-}$ *mice.* Current experiments are evaluating the effects Slack expression and knockout on parameters such mitochondrial membrane potential and metabolism in cell lines and neurons. Our findings indicate a dynamic relationship between Slack channels and the bioenergetics of neuronal mitochondria and suggest that Slack channel activity may regulate the synthesis of mitochondrial components.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

Support: NIH grant DC01919 to LKK
FRAXA grant

Title: Slack potassium channel inhibitors normalize behaviors and excess protein synthesis in Fmr1 knockout mice

Authors: Y. ZHANG[1], J. WU[2], H. WANG[3], I. H. QURAISHI[4], ***L. KACZMAREK**[5]; [1]Pharmacol., Yale Univ. Sch. Med., New Haven, CT; [2]Pharmacol., Yale Univ., New Haven, CT; [3]Dept. of Pharmacol., Yale Univ., New Haven, CT; [4]Dept. of Neurol., Yale Univ., NEW HAVEN, CT; [5]Yale Univ. Sch. Med., New Haven, CT

Abstract: Fragile X syndrome (FXS) is caused by the loss of FMRP (Fragile X Mental Retardation Protein), a polyribosome-associated RNA-binding protein encoded by the *FMR1* gene. While FMRP has multiple cellular actions, one canonical role of FMRP is to repress the synthesis of its mRNA targets, and reduction of FMRP levels in mice has been found to result in elevated protein synthesis coupled to loss of activity-dependent translation. In neurons from wild type animals, FMRP binds another translation regulator CYFIP1 (Cytoplasmic FMRP-Interacting Protein 1). The FMRP/CYFIP1 complex binds the translation initiation factor eIF4E, suppressing the translation of mRNAs bound to the complex. Both FMRP and CYFIP1 also bind the cytoplasmic domains of the Slack potassium channel, also termed KNa1.1 and KCNT1. Stimulation of Slack channels in neurons leads to the translocation of both regulators from eIF4E to the channel, triggering translation initiation. We have found that suppression of Slack channel by anti-sense oligonucleotides increases the binding of both CYFIP1 and FMRP to eIF4E. This suggests that, in *Fmr1* knockout animals, suppression of Slack may normalize mRNA translation by promoting the binding of CYFIP1 to eIF4E. To begin to test this hypothesis, we have investigated the effects of a Slack channel inhibitor, SLK-01, on behaviors in wild type and *Fmr1* knock out mice. We have found that 40mg/kg (IP) injection of SLK-01 rescues the ability of the *Fmr1* KO mice to recognize novel objects, such that the Discrimination Index in *Fmr1* KO mice treated with SLK-01 is significantly higher than that of *Fmr1* KO mice treated with carrier medium alone. In contrast, SLK-01 treatment had no effect on the wild type mice. Because anxiety and abnormal social behaviors are also prominent features of FXS in humans, we tested the effects of SLK-01 on social behavior in wild type and *Fmr1* KO mice. Our data shows that SLK-01 treatment improves social preference and increases social time in *Fmr1* KO mice, but it has no effect on these measures in wild type mice. These findings suggest that Slack inhibitors may be potential therapeutic agents to mitigate FXS symptoms. The findings from this study may also have broader implications for understanding the molecular mechanisms underlying other neurodevelopmental disorders characterized by dysregulated protein synthesis.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

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Topic: B.03. Ion Channels

Support: U54NS1088874

Title: Gain of function of KCNH1 induces hypoexcitability in cortical excitatory neurons derived from human induced pluripotent stem cells

Authors: *W. CHI[1], C. H. THOMPSON[2], N. CALLOW[1], H. ADIL[1], A. L. GEORGE, JR[2], E. KISKINIS[1];
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Abstract: *KCNH1* encodes Kv10.1 (ether-à-go-go, Eag1), the founding member of the EAG family of voltage-gated potassium (Kv) channels. Mutations in *KCNH1* have recently been identified in individuals with clinical presentation of epilepsy, intellectual disability (ID), or syndromic neurodevelopmental disorders. To study how *KCNH1* mutations affect the electrophysiological properties of human neurons, we introduced one recurrent mutation, I494V, to a reference induced pluripotent stem cell (iPSC) line using CRISPR/Cas9 technology. After quality control, we differentiated I494V and isogenic control iPSCs into cortical excitatory neurons and studied intrinsic neuronal excitability and network activity using whole-cell current clamp recording and multielectrode array (MEA), respectively. Whole-cell current clamp recordings showed that the I494V mutation causes a reduction in the resting membrane potential of neurons, consistent with its gain-of-function (GOF) nature previously established in heterologous systems. MEA-based analyses of populations of neurons showed that mutant I494V neurons exhibited decreased firing, bursting, and network bursting compared to isogenic controls. Notably, we found that treatment of the mutant *KCNH1* excitatory neurons with anti-sense oligonucleotides (ASOs) targeting *KCNH1* expression restored regular firing, establishing a causal relationship between neuronal and network hypoactivity and GOF of *KCNH1*. Together, this study establishes human neuronal models of KCNH1-associated disorders that can be used to investigate disease mechanisms and assess rational therapeutic modalities such as ASOs.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.09/B36

Topic: B.03. Ion Channels

Support: Kuwait University Research sector Grant YM01/23
Kuwait University College of graduate studies

Title: A Kv1.1 N-terminus mutation in a child with lower limb dystonia alters channel voltage-dependence and kinetics

Authors: N. ASWAD[1], S. AL-SABAH[2], ***S. M. K. HASAN**[1];
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Abstract: *KCNA1* on chromosome 12p13 is the gene encoding the 496 amino acids that make up the potassium voltage-dependent α-subunit Kv1.1. The Kv1.1 channel consists of four such α-subunits. Heterozygous point mutations in *KCNA1* that lead to Kv1.1 *loss-of-function* primarily cause episodic ataxia 1 (EA1; OMIM #160120). In this study, we investigate a previously reported *KCNA1* mutation (Set et al., 2017) in a child harboring an arginine to glutamine substitution at position 86 (p.R86Q) of the α-subunit's cytoplasmic N-terminus. The child did not present with typical episodic ataxia or myokymia symptoms but had lower limb stiffening and inability to walk. While mutations in the voltage-sensing and pore domains of Kv1.1 have been extensively investigated, we know very little about the functional consequence of residue substitutions in the N-terminus. We characterized the electrophysiological outcome of the p.R86Q mutation by expressing human Kv1.1 channels in *Xenopus laevis* oocytes. The N-terminal region is predicted to play a role in subunit tetramerization and proper channel assembly, yet mutated α-subunits were able to form functional channels that pass delayed rectifier currents. Oocytes that expressed only mutated α-subunits produced a significant reduction in Kv1.1 current and showed a positive shift in voltage-dependence of activation as previously observed with EA1 mutations located in the transmembrane segments of the Kv1.1 α-subunit. In addition, activation kinetics were significantly slower while deactivation was faster, implying a reduction in the time the channel spends in its open state. These findings show that the N-terminus plays a role in the channel's voltage-dependent activation and in its open state duration. Oocytes co-injected with both mutated and wild-type cRNA in equal amounts, to mimic the heterozygous condition of the disease, showed no difference in Kv1.1 current amplitude but still had significantly faster deactivation kinetics when compared to the wild-type channel. This may explain the milder symptoms observed in the child that dramatically improved with acetazolamide treatment. This study sheds light on the role of the N-terminus in Kv1.1 channel function and supports the emerging concept that a mutation's location within a channel's α-subunit influences the phenotype presented.

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Poster

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Program #/Poster #: PSTR438.10/B37

Topic: B.03. Ion Channels

Support: NICHD intramural research program

Title: Activity-dependent degradation of Kv4.2 contributes to synaptic plasticity and cognition in Angelman syndrome model mice

Authors: *J.-H. HU[1], C. MALLOY[2], Y. LIU[3], J. PARK[4], A. PRATT[1], M. A. WELCH[5], D. A. HOFFMAN[6];
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Abstract: Angelman syndrome (AS) is a severe neurological disorder characterized by intellectual disability, absence of speech, spontaneous seizure, and motor dysfunction. The absence of functional maternally derived UBE3A protein is considered the primary cause of AS, yet the downstream signaling pathways remain elusive. Here we identify the voltage-gated K^+ channel Kv4.2 as a seizure/activity-dependent substrate for UBE3A. We show that UBE3A ubiquitinates Kv4.2 at residue K103 and is required for activity-induced Kv4.2 protein loss in cultured hippocampal neurons. In a mouse model of AS, we observed elevated Kv4.2 protein level, abolished seizure-induced Kv4.2 ubiquitination and protein loss. AS mice also showed impaired dendritic gradient of Kv4.2 and reduced Kv4.2-DPP6 association. Further study revealed that UBE3A primarily targets DPP6 containing complex, consistent with a Kv4.2-p38-Pin1 mechanism. Moreover, deficits in mEPSC frequency and spike-timing-dependent LTP, as well as certain behaviors including cognitive inflexibility found in AS mice, were partially rescued when bred with Kv4.2 conditional knockout mice. These findings reveal a UBE3A downstream pathway regulating plasticity and cognitive behaviors, and provide potential targets for the treatment of AS.

Disclosures: J. Hu: None. **C. Malloy:** None. **Y. Liu:** None. **J. Park:** None. **A. Pratt:** None. **M.A. Welch:** None. **D.A. Hoffman:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.11/B38

Topic: B.03. Ion Channels

Title: Understanding the Differential Impact of K2P Channel Overexpression on the Cellular Membrane Potential

Authors: *Y. KIM[1,2], R. L. COOPER[3], D. MURRUGARRA[4];
[1]Biol., Univ. of Kentucky, Richmond, KY; [2]Model Laboratory School, Richmond, KY; [3]Biol., Univ. of Kentucky, Lexington, KY; [4]Mathematics, Univ. of Kentucky, Lexington, KY

Abstract: K2P channels (two-pore domain potassium channels) play an important role in cellular function by facilitating the flow of potassium ions across cell membranes to maintain cellular electrochemical balance. Their overexpression is commonly observed in cancerous cells, prompting questions regarding their role in cancer development or progression. Using the

Goldman-Hodgkin-Katz equation (measures the permeability and membrane potential based on the intracellular and extracellular values of important ions, including potassium, sodium, and chloride), this research aims to quantify membrane potential changes resulting from K2P channel overexpression, further developing physiological implications, which could lead to potential pharmaceutical treatments. The methodology involves overexpressing the K2P channels of a specific muscle line in Drosophila melanogaster (fruit flies). Having an experimental group of conducting K2P channels and a control group of nonconducting K2P channels, saline solutions with different potassium concentrations were used to insert microelectrodes into specific larval muscle cells (m6m7). Then, the membrane potential of the muscle cells was recorded based on responses in potassium permeability between nonconducting and overexpressing lines. Based on ten preparations, results suggested that overexpression of K2P channels increases its permeability to potassium, rendering the cell membrane potential more sensitive to potassium fluctuations. This increased sensitivity may contribute to differing activity patterns observed in cancer cells compared to healthier cells. By identifying selective blockers for certain K2P channels and understanding their sensitivity to other pharmaceutical agents, there's potential to target cancer cells specifically. However, achieving this requires further simulations using MATLAB by trying different fitting parameters in the Goldman-Hodgkin-Katz equation, which will result in a deeper understanding of how cells respond to overexpressing K2P channels.

Disclosures: Y. Kim: None. **R.L. Cooper:** None. **D. Murrugarra:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.12/B39

Topic: B.03. Ion Channels

Support: NSERC
CIHR
CRC
SK POP

Title: Innovating positive allosteric modulators of potassium channels to treat epilepsy

Authors: *T. KONG[1], J. ARSENAULT[2], Y. WENG[1], L.-Y. WANG[2,1];
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Abstract: Epilepsy is one of the most common neurological diseases that affects around 50 million people worldwide. The core substrate underlying the pathogenesis of epilepsy can be ascribed to an excitation and inhibition (E/I) imbalance at synaptic, circuit or system levels. Among numerous genetic mutations associated with epilepsy, ion channelopathy represents one of the leading causes for E/I imbalance by disrupting ion homeostasis and neuronal excitability.

Loss-of-function (LOF) mutations of the KCNA2 gene, encoding potassium channel Kv1.2, causes neurological diseases including severe epileptic encephalopathy, episodic ataxia type 1 (EA1), seizures and autism spectrum disorder. Nonetheless, no drugs are available to treat its LOF mutations.We hypothesize that targeting Kv1.2 channels with positive allosteric modulators (PAMs) can alleviate hyperexcitation phenotypes at cellular and system levels in Kv1.2 LOF mutation associated epilepsy and other neurodevelopmental disorders (NDDs) with hypoexpression of Kv1.2.We discovered a new class of positive allosteric modulators (PAMs), e.g. Compounds C1, C2 and C3, that potentiate Kv1.2 activity at nanomolar range. In the stable Kv1.2-GFP Chinese Hamster Ovary (CHO) cell-line, we investigated the effect of C1, C2 and C3 on Kv1.2 activity, expression, and localization. Electrophysiological recordings and *in silico* docking revealed that C2 has the highest potency among the analogs. Chronically, C2 and C3 promotes Kv1.2 trafficking to cytoplasmic membranes from the intracellular pool. Through *in silico* simulation and site-directed mutagenesis, we defined a novel binding cavity on the Kv1.2 channel for C2 and its structural analogs. In the cerebellum of *Fmr1*KO, a mouse model for Fragile X Syndrome, with known Kv1.2 hypoexpression phenotype in interneuron terminals, C2 attenuated hyperexcitability of interneurons and enhanced the spike frequency of Purkinje neurons (PNs) by reducing its inhibitory overtone. The effects of these PAMs in epilepsy treatment are explored in phosphatase and tensin homolog (*PTEN*) knockout (KO) human iPSCs derived neurons, linked to drug-resistant epilepsy. With multi-electrode array (MEA) recordings in PTEN-KO neurons, sub-micromolar of C2 showed therapeutic efficacy in supressing the hyperexcitability and burst activities in this epileptic model.This project rationalizes Kv1.2 PAMs as a viable approach to rectify the E/I imbalance in epilepsy. It will bring a new class of drugs to treat epilepsy and potentially other NDDs as a result of Kv1.2 channelopathy.

Disclosures: T. Kong: None. **J. Arsenault:** None. **Y. weng:** None. **L. Wang:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.13/B40

Topic: B.03. Ion Channels

Title: Simultaneous Measurement of PIP_2 and $K_V7.2$ Current in Single Cells

Authors: *N. GIZAW[1], C. H. THOMPSON[2], A. L. GEORGE, JR[3];
[1]Northwestern Univ., Evanston, IL; [2]Northwestern Univ., Chicago, IL, ; [3]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL.

Abstract: Simultaneous Measurement of PIP_2 and $K_V7.2$ Current in Single Cells
AuthorsNaomi B. Gizaw, Christopher H. Thompson, Alfred L. George, Jr.
DisclosuresNaomi B. Gizaw: None. Christopher H. Thompson: None. Alfred L. George Jr.: Grant funding from Biohaven Pharmaceuticals
Abstract

The membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) is an essential modulator of many ion channels including the voltage-gated potassium channel $K_V7.2$ encoded by the human gene *KCNQ2*. Pathogenic *KCNQ2* variants are associated with neonatal onset seizures with variable long-term neurodevelopment outcomes. $K_V7.2$ partners with the related channel subunit $K_V7.3$ to generate the neuronal muscarinic acetylcholine receptor modulated current (M-current), a slowly activating and deactivating current in central and peripheral neurons that opposes depolarization and dampens neuronal excitability. Muscarinic receptor activation leads to phospholipase C degradation of PIP_2 and suppression of M-current. The dependence of $K_V7.2$ current on intracellular levels of PIP_2 has been established by various pharmacological maneuvers but most studies have not directly correlated intracellular PIP_2 levels of channel activity measured by voltage clamp recording. In this study, we aimed to address that gap by direct measurement of PIP_2 levels simultaneously with whole-cell recording of $K_V7.2$ current in HEK293T cells. For this work we used the green fluorescent protein (GFP)-based PIP_2 biosensor dPlcR (Hertel, et al., PMID:31855412). HEK293T were co-transfected with 1 μg of biosensor plasmid and $K_V7.2$ cDNA allowing us to monitor both normalized current values and changes in fluorescence values over time in the same cells. Biosensor fluorescence in transfected HEK293T cells exhibited time-dependent decay when cells were treated with an inhibitor of PI3K-mediated PIP_2 synthesis (LY294002) or by activation of endogenous muscarinic receptors with acetylcholine. During extended whole-cell voltage-clamp recordings (20 minutes), $K_V7.2$ current measured in single cells runs down by 40% and this linearly correlated with time-dependent decay of biosensor fluorescence in the same cells ($p<0.0001$). We conclude that real-time correlation of $K_V7.2$ current with intracellular PIP_2 levels measured in single cells using a fluorescent biosensor is feasible. This approach will have value in studies of ion channel regulation by PIP_2.

Disclosures: N. Gizaw: None. **C.H. Thompson:** None. **A.L. George, Jr:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Grant funding from Biohaven Pharmaceuticals.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.14/B41

Topic: B.03. Ion Channels

Support: NIH NINDS 1R01NS126584-01A1

Title: The Targeting Mechanism and Function of Postsynaptic Kv7/KCNQ channels at Excitatory Synapse.

Authors: *S. MALPOTRA[1], G. C. TRACY[2];
[1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Mol. and Integrative Physiol., Univ. of Illinois At Urbana-Champaign, Champaign, IL

Abstract: Neuronal Kv7/KCNQ channels are voltage-gated potassium channels that produce slow-activating and non-inactivating outward potassium currents called I_M. Among 3 neuronal subunits (Kv7.2, Kv7.3, and Kv7.5), Kv7 channels are mostly heterotetramers of Kv7.2 and Kv7.3, both of which show overlapping and abundant distribution in the hippocampus and cortex, critical sites for cognition and behavior. In pyramidal neurons, they are highly expressed at the axonal plasma membrane including the axonal initial segment (AIS) where they potently limit repetitive firing of action potentials (AP), hyperpolarize the resting membrane potential, and regulate AP thresholds and properties. Consistently, their inhibition or deletion induces seizures, and mutations in Kv7.2 and Kv7.3 cause neonatal epilepsy including benign familial neonatal epilepsy (BFNE) and early-onset epileptic encephalopathy (EOEE). Surprisingly, recent immuno-electron microscopy (EM) studies in the primate prefrontal cortices revealed the presence of Kv7.2, Kv7.3, and Kv7.5 in the postsynaptic density (PSD) and dendritic spines that harbor the majority of excitatory synapses. *However, it is unclear whether Kv7.2 and Kv7.3 exist in dendritic spines of hippocampal pyramidal neurons, and if so, what are their roles in excitatory synaptic transmission.* In this study, we tested **the hypothesis** that Kv7.2 and Kv7.3 are present at excitatory synapses within dendritic spines of hippocampal pyramidal neurons, where their outward potassium current will suppress excitatory synaptic transmission. We have also investigated that Kv7.2 and Kv7.3 are present at excitatory synapses within dendritic spines of cortical neurons of Rat at Embryonic day 16. We have observed the expression of Kv7.3 alone at the excitatory synapses in the hippocampal and cortical neuronal cells at DIV16.Furthermore, we also aim to investigate if the interaction of Kv7.2 and Kv7.3 c-terminus of 190kD isoform of AnkG protein mediates their location and eventually expression at the postsynaptic spines.
Significance: Through this study, I expect to address how Kv7 channels localize to excitatory synapse and what their function is. Since cognitive deficit is linked to synaptic dysfunction, my study on EE mutations should increase our understanding of Kv7's role in EE-associated intellectual disability.

Disclosures: S. Malpotra: None. **G.C. Tracy:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.15/B42

Topic: B.03. Ion Channels

Support: NICHD Intramural Program

Title: Post-synaptic scaffold protein, Preso1, regulates the transient A-type potassium current and hippocampal CA1 excitability.

Authors: *M. WELCH, J. HU, D. A. HOFFMAN;
NIH, Bethesda, MD

Abstract: Intellectual disability (ID) is a neurodevelopmental disorder affecting 1-3% of the general population and is characterized by impairments in learning and adaptive behaviors. The underlying cause of ID is unknown, however, whole exome sequencing studies revealed mutations in the *Preso1* (aka *FRMPD4*) gene cause ID in humans. Preso1 (PSD-95-interacting regulator of spine morphogenesis) is a neuronal post-synaptic scaffold protein highly expressed in the hippocampus where it regulates spine development and excitatory synaptic transmission. Preso1 interacts with metabotropic glutamate receptors (mGluRs) and adjusts receptor signaling by recruiting proline directed kinases that modulate the interaction between the receptor and Homer, a mGluR regulatory protein. In this study, we show Preso1 regulates Kv4.2, the main A-type voltage-gated potassium channel in the hippocampus. We found Preso1 binds to Kv4.2 channels. To test if Preso1 has a functional effect on Kv4.2, the transient A-type potassium current, I_A, was recorded from outside-out patches pulled from CA1 pyramidal neurons in wild-type or Preso1 knock out (KO) mice. Knocking out Preso1 significantly reduced I_A by ~30% compared to wild-type control. We also performed whole-cell current clamp recordings to test whether CA1 excitability was affected, as Kv4.2 regulates hippocampal excitability. We found a significantly increased firing rate in the Preso1 KO mice, along with a more depolarized action potential (AP) threshold, higher AP amplitude, lower rheobase, and shorter latency to fire an AP. These changes in CA1 excitability are consistent with reduced Kv4.2 levels. Current studies are examining if synaptic properties and behavioral flexibility are altered in the Preso1 KO mice. In summary, this work identifies Kv4.2 as a novel target of Preso1 and shows hippocampal physiology is disrupted in Preso1 KO mice.

Disclosures: M. Welch: None. **J. Hu:** None. **D.A. Hoffman:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.16/B43

Topic: B.03. Ion Channels

Support: NIH Grant 5T32GM105538-10
NIH Grant 1F31NS135753-01

Title: An upstream open reading frame is a post-transcriptional repressor of KCNQ2 expression

Authors: *D. HUEY, C. G. VANOYE, C. Q. SIMMONS, Q. LI, E. K. STROUP, Z. JI, A. L. GEORGE, Jr.;
Northwestern Univ., Chicago, IL

Abstract: Heterozygous loss-of-function (LOF) is a common genetic mechanism among many monogenic epilepsy genes including *KCNQ2*, which encodes a voltage-gated potassium channel

subunit (Kv7.2) primarily expressed in the brain. Kv7.2 forms tetramers with Kv7.3 (encoded by *KCNQ3*) to generate the neuronal M-current, which opposes membrane depolarization and reduces neuronal excitability. Pathogenic variants in *KCNQ2* are associated with severe developmental and epileptic encephalopathies. In this study, we identified a single upstream open reading frame (uORF) within the 5'-untranslated region (5'-UTR) of the *KCNQ2* mRNA transcript by using ribosome profiling of human iPSC-derived neurons. Induced GABAergic neurons produced ribosome-protected reads mapping to the predicted-uORF, indicating actively translating ribosomes within the 5'-UTR. To investigate the effect of the uORF on translation, HEK293T cells were transfected with luciferase constructs containing the *KCNQ2* 5'-UTR and various single nucleotide mutations of the uORF start codon. Reporter gene assays of these cells revealed a 5-7-fold boost in protein translation ($p<0.005$) associated with mutations that disabled the upstream start codon, compared to the wild type 5'-UTR. A similar magnitude effect was observed with corresponding mutation of the mouse *Kcnq2* 5'-UTR. To assess channel function, CHO cells stably expressing Kv7.3 were transfected with a construct encoding a uORF-inactivated 5'-UTR and the full-length Kv7.2 coding sequence. Western blot and high-throughput voltage-clamp recording indicated 30% greater Kv7.2 protein levels ($p<0.05$) and two-fold greater M-current density ($p<0.005$) in cells transfected with the uORF inactivating mutation compared to the wild type 5'-UTR. No changes were detected in the mRNA levels of *KCNQ2* or *KCNQ3* by quantitative PCR. We concluded that the 5'-UTR of *KCNQ2* contains a functional uORF that post-transcriptionally represses translation of Kv7.2 *in vitro*. These findings identify a novel regulatory feature for Kv7.2 that could have physiological relevance, and might be a potential target for antisense oligonucleotides to enhance Kv7.2 expression.

Disclosures: D. Huey: None. **C.G. Vanoye:** None. **C.Q. Simmons:** None. **Q. Li:** None. **E.K. Stroup:** None. **Z. Ji:** None. **A.L. George:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.17/B44

Topic: B.03. Ion Channels

Support: NIH R44 MH119842
NIH NS011613
NIH 1R43NS125749

Title: Electronic expression of ion channel currents generated by the NEURON simulation program in stem cell-derived GABAergic neurons

Authors: B. K. PANAMA[1], S. ACHARYA[2], L. KORBEL[2], L. NILSSON[2], M. L. HINES[3], N. T. CARNEVALE[3], *R. L. RASMUSSON[1,2], G. C. L. BETT[1,2], M. W. NOWAK[2];
[1]SUNY at Buffalo, Buffalo, NY; [2]Cytocybernetics, Buffalo, NY; [3]Yale Univ., New Haven, CT

Abstract: The simulation program NEURON (www.neuron.yale.edu/neuron/) is widely used to generate computational models of neurons. This extensive body of in-silico cell and ion channels has been widely used. Enabling real-time computations in NEURON coupled to in vitro cell systems will open a myriad of new possibilities for interrogating neuronal cellular dynamics. We modified our dynamic clamp to interface with NEURON, allowing for the direct addition of individual NEURON ion channel model currents into living cells. We performed patch-clamp electrophysiological recordings of human stem cell-derived GABAergic neurons (hiPSC-GNs) (Fujifilm Cellular Dynamics) using the whole-cell configuration. The low background K^+ current expression typically observed in hiPSC-GNs results in depolarized resting membrane potentials (RMP), -30.2±1.1 mV (mean±SEM, n = 15), which leads to the unstable action potential behavior (APs). The electronic expression of a Cybercyte (Cytocybernetics) K^+ background current, modeled after the Goldman-Hodgkin-Katz equation (I_{GHK}), allowed the tuning of the RMP to more hyperpolarized potentials (-56.4±0.6 mV, n=12) and allowed for a physiological AP to be evoked. We coded a NEURON mod file that produced a similar I_{GHK} /K^+ channel current for electronic expression in the hiPSC-GNs. As with the Cybercyte, I_{GHK}/K^+ model, virtual expression of the NEURON I_{GHK}/K^+ conductance hyperpolarized the RMP to -57.4±0.5 mV (n=8) and the ability to record evoked APs. We also expressed two additional voltage-gated K^+ channel currents, Kv1 and Kv4, from a NEURON Purkinje neuron model (Akemann and Knopfel, 2006; https://modeldb.science/). The electronic expression of Kv1 and Kv4 hyperpolarized the RMP to -55.4±0.6 mV (n=8) and -58.8±1.0 mV (n=8) respectively, restoring the physiological evoked AP morphology (Kv1: AP amplitude = 72±4.3 mV; AHP amplitude = 20.5±3.6 mV, APD90 = 2.5±0.3 ms; Kv4: AP amplitude = 75±6.3 mV; AHP amplitude = 14.6±3.5 mV, APD90 = 2.6±0.2 ms) (n=8). Given the extensive NEURON model database, interfacing a dynamic clamp system with NEURON allows electrophysiologists access to well-tested and documented ion channel models for virtual expression in living cells and direct comparison to predicted pure in silico cellular results.

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Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.18/B45

Topic: B.03. Ion Channels

Support: the National Natural Science Foundation of China (32071040 to BL, 82071241 and 81871048 to LH)
Guangdong Basic and Applied Basic Research Foundation

(2023B1515040019 to BL)
Guangdong Project (2017GC010590 to BL)

Title: An optogenetic toolbox for tunable control of endogenous ion channels

Authors: *L. CHEN[1], X. ZHANG[2], L. HUANG[2], B. LI[3];
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Abstract: Ion channels mediate ions flow through the membrane and play a key role in neuronal signaling transduction. States of ion channels change dynamically under different physiological and pathological conditions. However, fast and genetically encoded tools to regulate endogenous ion channels are lacking. Here, we developed two optogenetic tools for the BK channel:(1) LIICA$_{BK}$ (**L**ight-**i**nduced **i**on **C**hannel **A**ctivator, LIICA) by fusing light-sensitive LOV2 domain with BK channel-specific binding peptide, and (2) BK-lumi, a light-sensitive toxin peptide. We demonstrate that our optogenetic tools can modulate endogenous BK channels from in vitro to in vivo, offering a powerful approach to investigate function of subcellular endogenous ion channels.

Disclosures: L. Chen: None. **X. Zhang:** None. **L. Huang:** None. **B. Li:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.19/B46

Topic: B.03. Ion Channels

Support: NSF IOS-2212750
NIH R01 NS130917

Title: In-vivo electrophysiological characterization of an inactivating potassium conductance in a collision-detecting neuron

Authors: *G. SHAULSKY, R. B. DEWELL, F. GABBIANI;
Baylor Col. of Med., Houston, TX

Abstract: In grasshoppers, visual detection of approaching predators is accomplished by the Lobula Giant Movement Detector (LGMD). The LGMD is an identified neuron in the optic lobe that integrates retinotopic inputs originating from every facet of the eye within a large dendritic field, called dendritic field A. An inactivating K^+ conductance in the LGMD is critical to discriminate the spatial coherence of black looming stimuli. This conductance has been hypothesized to resemble the slowly inactivating K_D in mammals based on compartmental model simulations. Here, we show that the K^+-conductance is localized in dendritic field A, and characterize its kinetics. We performed intracellular sharp electrode recordings in awake animals

and applied depolarizing steps in voltage clamp before and after pharmacological blockade, with the difference in responses showing the expected slowly-inactivating potassium conductance. We varied the magnitude of the steps to characterize the voltage dependence and fit exponential curves to these subtractive traces to estimate the time constants of both activation and inactivation. A detailed NEURON model of the LGMD including a Hodgkin-Huxley type K^+ conductance with the experimentally-determined properties simulated visual responses, recapitulating previous experimental visual results. This research highlights the ability of the grasshopper model system to link electrophysiological mechanisms with ethologically-relevant sensory discrimination.

Disclosures: G. Shaulsky: None. **R.B. Dewell:** None. **F. Gabbiani:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.20/B47

Topic: B.03. Ion Channels

Support: R01DA053070

Title: Unique Role of Calcium-Activated Potassium (BK) Channels After Fentanyl Self-administration in the rat

Authors: *F. WU[1], J. SHAYKIN[2], N. PANDEY[3], P. I. ORTINSKI[3];
[1]Neurosci., Univ. of kentucky, Lexington, KY; [2]Psychology, [3]Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: The escalation of fentanyl use presents a continuing public health crisis in the US. Cellular responses to opioids in laboratory animals and humans involve potassium channels. However, which of the many potassium (K^+) channel groups may underlie cellular and behavioral plasticity associated with fentanyl self-administration remains unclear. Our study focused on investigating whether escalation of fentanyl intake recruits a unique sub-population of K^+ channels to impact neuronal excitability in the infralimbic prefrontal cortex (IL) and the nucleus accumbens shell (NAc). Male and female rats underwent jugular catheterization and assigned to one of three groups: contingent fentanyl, yoked fentanyl, and yoked saline. Following 19 days of fentanyl or saline administration in long-access (4 hrs) daily sessions, animals were sacrificed for brain extraction and brain slice preparation. Using whole-cell patch-clamp techniques, we isolated activity of six distinct groups of K^+ channels in the IL and the NAc neurons by applying channel-specific antagonists. Escalation of fentanyl seeking was observed in the contingent fentanyl group as expected from prior literature. Preliminary results indicate that rats exposed to either contingent or yoked fentanyl display increased amplitude of calcium-activated, BK, channel-mediated current in the IL, compared to yoked saline controls. No significant differences were detected for currents mediated by the calcium-activated SK

channels, delayed rectifier K^+ channels, A-type K^+ channels, M-type K^+ channels, and two-pore domain K^+ channels. Together, these results suggest a unique association between calcium-activated K^+ channels and fentanyl exposure. However, escalation of fentanyl seeking behavior could not be linked to a unique K^+ channel activity profile. Ongoing experimentation aims to further investigate the association between BK channels and calcium signaling in IL and additionally explores a potential association between fentanyl seeking and activity of G-protein coupled inward rectifier K^+ channels.

Disclosures: F. Wu: None. **J. Shaykin:** None. **N. Pandey:** None. **P.I. Ortinski:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.21/B48

Topic: B.03. Ion Channels

Support: R01-ES031407

Title: Cerebrovascular smooth muscle BK channels participate in toluene-induced constriction of brain arteries.

Authors: *A. A. SHAW[1], J. D. STEKETEE[2], A. BUKIYA[3], A. DOPICO[4];
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Abstract: Toluene acute intoxication by inhalation and brain ischemia share many neurological and psychological outcomes. Since cerebral artery constriction is well-known to cause brain ischemia, we hypothesized that toluene at concentrations reached during acute intoxication following inhalation constricted cerebral arteries. To test this, we determined toluene in vivo and ex vivo actions on the diameter of middle cerebral arteries (MCA) and its pial branches in rats, as brain circulation in this species shares many features with that of humans, including the fact that MCA irrigates the largest portion of the brain. Male and female Sprague-Dawley rats (250-400 g) were anesthetized with ketamine/xylazine mixture prior to cranial window surgery and diameter of MCA-originated pial arteries was determined immediately before and after rats were placed in a closed inhalation chamber where 1.2 mL of toluene was dispensed on a paper towel. Rats were exposed to toluene for 1, 5, 10, 20, or 30 minutes and toluene levels in the air were determined at the end of each exposure by an infrared analyzer. In both sexes, toluene (1,000–10,000 ppm) evoked a concentration-dependent reduction in artery diameter, with average peak arterial constriction reaching 8.5% of pre-toluene values, extending initial data (*Shaw et al., SfN 2023*). Exposure to 1,000-10,000 ppm rendered blood toluene levels of 3-65 mM as determined by gas chromatography. Next, we addressed whether toluene action remained in absence of

circulating, metabolic, systemic, and endothelial factors by applying toluene to both endothelium-intact and de-endothelialized, isolated MCA segments. Animals were anesthetized as described above, and MCA diameter was determined under pressurization at 60 mmHg which develops physiological myogenic tone. Toluene was perfused onto the isolated MCA at 0.0003, 0.001, 0.01, 0.1, 1, or 3 mM final concentration after sonication into physiological saline. Toluene application resulted in concentration-dependent vasoconstriction as was found in vivo. To test the involvement of big conductance Ca^{2+}/voltage-gated K^+ (BK) channels in toluene-induced MCA constriction, we probed MCA from *KCNMA1*$^{-/-}$ mice, which do not express BK channels. Whether when evaluated in vivo or ex vivo, toluene vasoconstriction was significantly reduced in these mice. Our data document for the first time that toluene at concentrations during intoxication in humans upon recreational use constricts MCA and its branches by involving arterial smooth muscle BK channels, an action that very likely contributes to toluene-induced brain ischemia.

Disclosures: A.A. Shaw: None. **J.D. Steketee:** None. **A. Bukiya:** None. **A. Dopico:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.22/B49

Topic: B.03. Ion Channels

Support: funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Channelome: Towards the drug screening paradigm shift

Authors: *E. LOGETTE, R. RANJAN, K. H. ARULKANDARAJAH, M. JOFFRAUD, A. JOURNE, K. JOHNSTON, M. HERZOG, E. SCANTAMBURLO, S. VAN DORP, H. MARKRAM;
Blue Brain Project, Brain Mind Inst., EPFL, Lausanne, Switzerland

Abstract: Voltage-gated ion channels (VGICs) are highly specialized proteins responsible for generating and regulating electrical signals across cell membranes. These channels play a crucial role in maintaining the proper functioning of various cells and organs, making them key targets for research in cell physiology, drug discovery, and quality control. For many years, the manual patch-clamp method has been the gold standard for studying the biophysical properties of ion channels. However, this manual technique is limited in its ability to simultaneously investigate more than a few ion channels, making it difficult to conduct extensive research or drug screening on all VGICs.The advent of automated patch-clamp systems has revolutionized the field by enabling daily recordings from thousands of cells. Despite these advancements, many contemporary research questions still rely on conclusions drawn from older, more limited

experiments. For example, compounds tested on only a handful of ion channels are often cited as "specific blockers" in prestigious research journals. Similarly, drugs are sometimes prematurely classified as non-interacting after being screened against only a subset of ion channels. Given the critical role of VGICs in ensuring drug safety and efficacy, it is crucial to test drugs thoroughly. However, even major pharmaceutical companies often assess numerous drug candidates against only a select group of ion channels instead of testing a single drug against all VGICs. In this study, for comparative analysis with published ion channel literature, we developed a ChatGPT-based AI tool to screen the effects of a drug on all VGICs. This AI tool offers a first-of-its-kind comprehensive understanding of a drug's reported impact on all VGICs. In parallel, we used in-house generated library of ion channels expressing stable CHO cell lines in Ready-to-Record form and a high-throughput automated patch-clamp robot for drug screening. Our goal is to provide the first drug screening map across all major VGICs, demonstrating the feasibility of expansive and holistic drug testing.

Disclosures: E. Logette: None. **R. Ranjan:** None. **K.H. Arulkandarajah:** None. **M. Joffraud:** None. **A. journe:** None. **K. Johnston:** None. **M. Herzog:** None. **E. Scantamburlo:** None. **S. Van Dorp:** None. **H. Markram:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.23/B50

Topic: B.03. Ion Channels

Support: funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Channelome: A Comprehensive Resource For Voltage-Gated Ion Channel Kinetics

Authors: *R. RANJAN[1], E. LOGETTE[1], S. VAN DORP[1], K. H. ARULKANDARAJAH[1], M. HERZOG[1], M. JOFFRAUD[1], E. SCANTAMBURLO[1], A. JOURNE[1], K. JOHNSTON[1], D. MANDGE[2], H. MARKRAM[1];
[1]Blue Brain Project, Brain Mind Institute, EPFL, Lausanne, Switzerland; [2]Biosci. and Bioengineering, Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL), Geneva, Switzerland

Abstract: Voltage-gated ion channels (VGICs) are integral membrane proteins that allow the flow of ions across the cell membrane, playing a crucial role in generating and transmitting electrical signals in excitable cells like neurons and muscle cells. Accurate characterization of VGICs biophysical properties, particularly their voltage and temperature dependence, is fundamental for constructing precise mathematical models and understanding their physiological roles. Despite over four decades of research on ion channels, kinetic characterization has been

limited to a few channels studied under broad experimental conditions and often at non-physiological temperatures, resulting in a lack of standardized kinetic data. Additionally, the absence of shared raw experimental data further compounds this issue. To address this gap, we started with the kinetic characterization of 40 voltage-gated potassium channels in a study published in 2019. Today, we present a comprehensive and systematic exploration of the biophysical properties of all major voltage-gated ion channels, spanning Kv, K2P, Kir, KCa, Nav, Cav, and HCN channels. Using stable cell lines and automated patch-clamp systems, we obtained temperature-dependent biophysical data on those VGICs that were previously absent from the literature. The stable cell lines and reference kinetic data are now also being used to screen the effect of a single drug across all main VGICs. All electrophysiological data, combined with meticulously curated information from the existing literature, are now accessible to the scientific community through an updated web application called Channelpedia. We proudly introduce this resource as the Channelome, which represents a milestone in the pursuit of comprehensive and standardized VGIC kinetic data.

Disclosures: R. Ranjan: None. **E. Logette:** None. **S. Van Dorp:** None. **K.H. Arulkandarajah:** None. **M. Herzog:** None. **M. Joffraud:** None. **E. Scantamburlo:** None. **A. journe:** None. **K. Johnston:** None. **D. Mandge:** None. **H. Markram:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.24/B51

Topic: I.06. Computation, Modeling, and Simulation

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology.

Title: Biophysically detailed cortical neuron models with genetically-defined ion channels

Authors: *D. MANDGE, R. RANJAN, E. LOGETTE, T. DAMART, A. T. JAQUIER, L. KANARI, D. KELLER, Y. ROUSSEL, S. VAN DORP, W. VAN GEIT, H. MARKRAM; Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL), Geneva, Switzerland

Abstract: Neocortical neurons can be classified into different electrical firing types (e-types). A common approach to modeling e-types involves creating detailed electrical models (e-models) using generic ion channel currents such as transient and persistent sodium, potassium channels, and high- and low-voltage activated calcium channels. While this approach accurately captures a neuron's electrical behavior, it does not establish a link between specific ion channels and observed electrophysiological properties. However, if we model the neuron using only the ion channels known to be expressed in that cell, based on single-cell gene expression data, it would be possible to trace causal events down to specific ion channel genes. The main obstacle with

this approach has been the lack of ion channel models for the different genetic subtypes of ion channel genes. To this end, we systematically characterized the kinetics of all voltage-gated ion channels and then built biologically accurate Hodgkin-Huxley models from experimental data. We used these genetic channel models to construct e-models in this study. We optimized model parameters, specifically ion channel conductance, by minimizing differences between the e-model and targeted experimental data across a defined set of electrophysiological features. These genetic models reproduce firing properties observed in in vitro recordings and establish a link between single-cell gene expression data and neuron modeling, leading to a better understanding of neuron electrophysiology. Ultimately, these models can be used for disease simulations and in silico drug screening.

Disclosures: D. Mandge: None. **R. Ranjan:** None. **E. Logette:** None. **T. Damart:** None. **A.T. Jaquier:** None. **L. Kanari:** None. **D. Keller:** None. **Y. Roussel:** None. **S. Van Dorp:** None. **W. Van Geit:** None. **H. Markram:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.25/Web Only

Topic: E.09. Motor Neurons and Muscle

Support: Chellgren Endowed Funding
University of Kentucky Office of Undergraduate Research
Research Priority Areas
Personal Funding (R.L.C)

Title: The behavioral effects of overexpression of K2P channels in various neuronal types found in larval and adult Drosophila

Authors: *A. C. TAUL[1], E. ELLIOTT[1], R. L. COOPER[2];
[1]Univ. of Kentucky, Lexington, KY; [2]Dept Biol, Univ. of Kentucky, Lexington, KY

Abstract: Two-pore-domain K+ channels (K2P) are responsible for maintaining the resting membrane potential of cells. Prior to further identification, these were referred to as leak channels. There appears to be 15 known types of K2P channels in humans and 11 known types in Drosophila, as well as six subfamilies, although little is known about the expression of these subtypes in various animal tissues or the impact of altered expression on cellular physiology. The Drosophila model allows for selective misexpression of certain neuron subsets, providing insight into individual cell types and the animal's physiology as a whole. It is established that glial cells within the nervous system play an important role in the development and function of the nervous system, as they release gliotransmitters and cytokines. Prior research on overexpressed glial K2P channels and their impacts on behavior and neuronal function was limited, but yielded results that were uncharacteristic of the model. This project expands upon prior research conducted of

Drosophila pan-glia cells and motor neurons to examine the effects of K2p overexpression on behavior and physiology. After conducting various assays, it was concluded that overexpression in motor neurons had the most prominent effects on Drosophila functioning; with glial, sensory, and chordotonal neurons also generating statistically significant differences in Drosophila activity. Overall, it appears that overexpression of K2P channels seems to alter behavior.

Disclosures: A.C. Taul: None. **E. Elliott:** None. **R.L. Cooper:** None.

Poster

PSTR438: Voltage-Gated Potassium Channels: Signaling, Function and Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR438.26/B52

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant 3R35NS097343

Title: A novel conductance-based model of plateau generation

Authors: *M. KENNGOTT[1], E. E. MARDER[2], P. SENGUPTA[3];
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Abstract: Plateau potentials are an important but incompletely explored mode of electrical activity in excitable cells, which produce a bout of depolarization that persists long after the end of the precipitating stimulus. This bistability allows the membrane potential to function analogously to an electrical flip-flop, allowing the membrane to stably occupy distinct electrical states. Plateaus serve many physiological functions, from short term state memory to the production of rhythmic movements, and are also implicated in pathologies associated with chronic injuries. It is therefore important to understand the full range of mechanisms that generate plateau potentials as well as their functional significance. We present a new model of a plateau system based on pharyngeal pumping in C. elegans. The model includes a leak current, a synaptic current, a T-type Ca2+ current, a slowly-inactivating L-type Ca2+ current, and a novel K+ current exhibiting ultrafast inactivation. We performed sensitivity analysis of this model to varying sets of maximal conductances. This analysis reveals that the plateau duration is robustly set by the balance between the L-type conductance and the K+ current, allowing in principle for plateaus of arbitrary duration. Furthermore, unlike the canonical delayed-rectifier K+ conductance, the unusual electrophysiology of the K+ channel presented here allows it to activate independently of the plateau duration, delivering extremely rapid repolarization, a crucial feature for the feeding strategy of C. elegans.

Disclosures: M. Kenngott: None. **E.E. Marder:** None. **P. Sengupta:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.01/B53

Topic: B.04. Synaptic Transmission

Title: The Neural Synapse as a Transistor: A 21st Century Conceptual Framework

Authors: *R. C. DOBSON[1,2];
[1]Dept. of Electrical Engin., Rochester Inst. of Technol., Rochester, NY; [2]Osher Lifelong Learning Institute, Rochester Institute of Technology, Rochester, NY

Abstract: Around 1950 Bell Labs apposed two semiconductors (SCs) to create the first Bipolar Junction Transistor (BJT). Subsequent refinement revolutionized our technological world. Apposing 2 synaptic membranes creates a similar structure.
A basic PNP BJT requires 5 components: 2 P substances deficient in electrons which surround an N substance with excess electrons; a depletion zone (DZ) at the PN junction; and, an intrinsic power supply. The double bilayer lipid membrane synapse contains chemical structures that provide the corresponding parts.
With established concepts and current scientific observations, the neural synapse (NS) (NOT the neuromuscular one) can be described as a Common Base, Reverse Bias, PNP BJT, with the electron as a signal transmitter, and "neurotransmitters" (NTs) acting as essential neuroMODULATORS.
Key Facts in this model: 1. Docosahexaenoic Acid (DHA), with 6 π bonds, is a critical part of the synapse in ALL species with a nervous system, across all time. Without it, the nerves do not work. DHA, with its unique chemical and electronic structure, lies with its carboxyl group within the lipid polar head (PH), and the α-π orbital (π closest to carboxyl) close to the PH. DHA maintains an all-cis isomer, but can change conformations, each with its own energy level, or band, within picoseconds. 2. The α-π bond in unsaturated organic SCs interacts with the metallic N material to enable SC action in synthetic systems. The α-π in DHA is positioned to do the same. 3. The synaptic cleft is not empty. It contains organized material, most likely liquid crystalline H2O.
The synaptic Common Base, Reverse Bias, PNP BJT model: 1. The 2 P substances are the acyl lipid chains. 2. The N substance comprises the PH from the two apposed synaptic membranes + structured H2O in the cleft. 3. Intrinsic power arises from the chemical reaction: Glutamate- —> GABA + CO2 + e-. The reaction occurs on the outer BLM, but the electron is transmitted quantum mechanically to the interior of the axon. Other "NTs" act as essential neuromodulators, e.g., the NMDA receptor can modulate e- production, thus adjusting the electrical bias of the synapse. 4. The DZ is formed by charge separation across the PN junction. In the NS the α-π orbital of DHA can interact with the polar head and the remaining acyl chain, allowing negative charge to migrate into the P region (perturbation of molecular orbitals). Alternatively, conformational change of DHA may affect charge distribution between the Highest Occupied and Lowest Unoccupied Molecular Orbitals.

These individual components can be assembled into the complete Synaptic PNP BJT. Expansion of SC concepts in neuroscience can lead to new insights about neural function.

Disclosures: R.C. Dobson: None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.02/B54

Topic: B.04. Synaptic Transmission

Title: Exploring the role of Neurexin-Neuroligin in the specification of synapses vulnerable to erasure in sensory-motor neurons of Aplysia

Authors: *E. AMOAH[1], T. W. DUNN[2], W. S. SOSSIN[3];
[1]Neurol. and Neurosurg., McGill Univ., Montréal, QC, Canada; [3]Dept Neurobiol, [2]McGill Univ., Montreal, QC, Canada

Abstract: Synapses constitute highly specialized sites of asymmetric cell-cell adhesion and intercellular communication. One model for memory maintenance is through the generation of specialized synapses. To account for the vulnerability of memory to recall and pharmacological disruption, these synapses would be vulnerable to erasure and thus have specific complements of proteins that define this function. One model used to examine this hypothesis is sensory-motor neuron cultures of Aplysia, where long-lasting increases in synaptic strength (long-term facilitation; LTF) can be erased by blocking reconsolidation after reactivation or by treatment with the zeta inhibitory peptide (ZIP) or by expression of dominant negative protein kinase Ms. Specializedsynapses imply specific synaptic organizers and previous work has implicated Aplysia neuroligin(ApNLG) and neurexin (ApNRXN) in organizing synapses required for LTF in Aplysia sensory-motor neuron synapses. To determine if synapses organized by ApNRXN and ApNLG aresynapses vulnerable to erasure requires live imaging of these synapses. To accomplish this, we inserted a bungarotoxin binding site in the extracellular domain of ApNRXN and labelled the extracellular ApNRXN clusters with fluorescent bungarotoxin. This method allowed us to confirm the surface expression of ApNRXN characterized by punctate patterns along the neurites. Moreover, simultaneous overexpression of ApNRXN in sensory neurons and blue fluorescent protein (BFP) tagged ApNLG in motor neurons shows colocalization of ApNRXN clusters withBFP-ApNLG, and this expression was coupled to an increase in synaptic strength. However, theApNLG constructs generated by our lab differ from those used in the previous study (Choi et al.,2011. *Neuron*, *70*(3), 468-481. https://doi.org/10.1016/j.neuron.2011.03.020). In the previous study, the initial sequence ApNLG was cloned using 3'RACE. However, the product of the RACE PCR is found on a genomic scaffold different from the rest of the gene and has no homology to other molluscan neuroligin sequences. In contrast, we found a good match to other molluscan neuroligins in the new Aplysia transcriptome, and it is contiguous with the previously cloned region of Neuroligin in the

genome. To determine if the colocalized ApNLG and APN-RXN puncta are synapses, we will determine if these clusters colocalize with Excitatory PostSynaptic Calcium Transients (EPSCATs) that we have shown mark synapses in these cultures. Finally, we will determine if ZIP erases the EPSCaTs associated with ApNRXN-APNLG clusters.

Disclosures: E. Amoah: None. **T.W. Dunn:** None. **W.S. Sossin:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.03/Web Only

Topic: B.04. Synaptic Transmission

Support: NIH Grant R00 MH118425
NARSAD BBRF Young Investigator Award

Title: Directly visualizing the endogenous localization of the synaptic adhesion molecules, MDGA1 and MDGA2, in the hippocampus for the first time

Authors: *M. SANDOVAL, L. ACOSTA SOTO, J. DÍAZ-ALONSO;
Anat. and Neurobio., UC Irvine, Irvine, CA

Abstract: The MAM domain-containing glycosylphosphatidylinositol (GPI) anchor proteins 1 and 2 (MDGA1 and MDGA2) are extracellular, GPI-anchored synaptic adhesion molecules, making them highly motile - only transiently entering the postsynaptic density. However, MDGA1 and MDGA2 have been shown to act as inhibitory and excitatory synapse repressors, respectively. In addition to these seemingly contradictory properties, due to the lack of suitable antibodies against MDGA1 and MDGA2, the in vivo localization, developmental pattern of expression, and therefore accurate investigation of their roles in synaptic transmission itself have been hindered. Here, we generated a knock-in (KI) mouse line expressing epitope-tagged MDGA1 and MDGA2 under endogenous control. Utilizing this model, we quantified their developmental protein expressions and subcellular localizations for the first time. We found that endogenous MDGA1 and MDGA2 expression gradually increases postnatally, peaking around P15 before sharply decreasing after P22 (n = 3/4 mice). We similarly characterized MDGA1/2 expression across the P15 mouse brain via brain region-specific lysates, showing high levels of expression of both molecules in the hippocampus (n = 3/4 mice). Next, we used these KI mice to visualize the colocalization of immunolabeled HA-MDGA1 and Myc-MDGA2 puncta with 2 postsynaptic markers (Homer1b/c and NLGN2) and each other in area CA1 and Dentate Gyrus (DG) of the hippocampus (n = 6 KI mice/marker). KI samples of both sexes were processed near the peak of MDGA1 expression on postnatal day 20 (P20). In CA1 - via super resolution microscopy (SIM) - we found that HA-MDGA1 and Myc-MDGA2 immunolabeled puncta do not qualitatively occupy the same neuronal compartments, indicating dissimilar localization and possibly confirming non-synaptic segmentation. Ongoing work is focused on quantifying this

colocalization as well as that with postsynaptic markers to elucidate their endogenous localization, providing much-needed foundational understanding about these proteins. We are concurrently assessing the functional roles of MDGA1 and MDGA2 in early postnatal hippocampal development. Using sparse, CRISPR-mediated KO, we are performing dual whole-cell patch clamp recordings in acute mouse slices of P15-P28 mice, targeting peak MDGA1/2 expression. We are assessing changes in inhibitory and excitatory synaptic transmission and long term potentiation (LTP) at CA3->CA1 synapses. Overall, our data expands our understanding of the localization and function of endogenous MDGAs, highlighting their importance in the complicated processes governing synaptic homeostasis.

Disclosures: M. Sandoval: None. **L. Acosta Soto:** None. **J. Díaz-Alonso:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.04/B55

Topic: B.04. Synaptic Transmission

Support: NINDS Intramural Funds

Title: Presynaptic and postsynaptic molecular complexes linked by transsynaptic assemblies, visualized by electron tomography

Authors: *A. COLE[1], T. S. REESE[2];
[1]NINDS, Bethesda, MD; [2]NINDS, NIH/ NINDS, Bethesda, MD

Abstract: At the chemical synapse, complex molecular interplay enables neuronal communication. Mapping the distribution and interactions of proteins within individual compartments has been crucial to our understanding of synaptic transmission. Both light and electron microscopy have documented alignments of key synaptic proteins across the synaptic cleft, suggesting coordination between compartments. Our 3D renderings, derived from electron tomograms of high-pressure frozen and freeze-substituted dissociated rat hippocampal cultures, reveal synapse-spanning complexes termed transsynaptic assemblies. These assemblies, consisting of connected electron dense structures across synaptic compartments, suggest a modular nature consistent with established inter-compartmental molecular binding behaviors. A cross-section of a synapse approximately 100 nm thick contained as many as 77 assemblies, with 20 percent of these assemblies connected to synaptic vesicles. Each synaptic compartment contains a distinct set of structures integrated into transsynaptic assemblies, with some presynaptic and postsynaptic components connecting to multiple assemblies, linking them into larger domains of association. We describe the morphologies of typical intracellular components and assemblies and map their distribution within the synapse. We propose that these assemblies could serve as modular structures, composed of an array of molecules or complexes that form a structural unit. The modular arrangement might facilitate the coordination and maintenance of

key materials necessary for various synaptic functions, contributing to a well maintained yet fast adapting synapse.

Disclosures: A. Cole: None. **T.S. Reese:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.05/B56

Topic: B.04. Synaptic Transmission

Support: AFOSR grant FA9550-20-0061

Title: Ca^{2+}activity evoked by nanosecond electric pulses in GCaMP6F-expressing chromaffin cells in murine adrenal gland slices

Authors: C. VIOLA[1], N. M. PROCACCI[1], N. LEBLANC[1], **J. ZAKLIT**[4], T. W. GOULD[2], *G. CRAVISO[3,1];
[1]Pharmacol., [2]Physiol. and Cell Biol., [3]Univ. of Nevada Reno Sch. of Med., Reno, NV;
[4]Electrical and Biomed. Engin., Univ. of Nevada Reno, Reno, NV

Abstract: Electrical stimulation continues to gain momentum as a treatment modality, with novel approaches being sought that have the potential for precise targeting of *in vivo* sites *non-invasively*. We have shown that nanosecond electric pulses (NEP), which have this potential, evoke Ca^{2+}-dependent exocytosis in cultured adrenal chromaffin cells (CC). To evaluate the effectiveness of NEP to stimulate CC in intact tissue, we exposed 100 µm thick slices of adrenal glands, obtained from 8 to 12-week-old male and female transgenic mice that conditionally express GCaMP6f in CC, to 30 ns pulses. Slices were placed in a laminar perfusion chamber that was placed on the stage of an upright fluorescence microscope and filled with an oxygenated balanced salt solution (BSS) maintained at 37°C. A tissue anchor was placed on top of the slice, with the pair of tungsten rod electrodes that delivered the NEP positioned over the top of the tissue anchor. A space of 200 µm separated the electrodes, enabling a field of view at 20X magnification that included almost all of the medulla. A single pulse elicited a rapid and transient (half-width 5 s) rise in intracellular Ca^{2+} in CC ranging from 1.5 to fivefold that was absent in Ca^{2+}-free BSS. The response was similar to that evoked by bath application of the nicotinic receptor agonist 1,1-dimethyl-4-piperazinium (5 µM). As determined by ANOVA analysis, reproducible stimulation of CC with NEP trains (i.e., Ca^{2+} responses evoked by each pulse in the train were not significantly different with respect to time-to-peak of the response, response amplitude and half-width) was achieved when the interval between pulses was 20 to 30 s. Shorter interpulse intervals caused diminished Ca^{2+} response amplitudes, longer half-widths of responses and an increase in baseline. Tetrodotoxin had no effect, indicating that the pulse-induced rise in intracellular Ca^{2+} did not involve activation of voltage-gated Na^{+} channels present on either splanchnic nerve endings that innervate CC or on CC themselves. Blocking nicotinic receptors

with hexamethonium (100 µM) had no effect either, suggesting NEP stimulation targeted CC directly. Finally, NEP stimulation did not alter spontaneous Ca^{2+} activity. These findings highlight the ability to target GCaMP6f expression to mouse adrenal CC for studying the effects of NEP stimulation on CC excitability *in situ*, which will aid future studies investigating underlying mechanisms and how these mechanisms compare with those elicited by conventional electrical stimulation.

Disclosures: C. Viola: None. **N.M. Procacci:** None. **N. Leblanc:** None. **J. Zaklit:** None. **T.W. Gould:** None. **G. Craviso:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.06/B57

Topic: B.04. Synaptic Transmission

Support: Pritzker Consortium #87000081

Title: The role of obsessive compulsive disorder-gene SLITRK5 in BDNF-dependent synaptic plasticity

Authors: *S. MARTINELLI, F. S. LEE;
Psychiatry, Weill Cornell Med., New York, NY

Abstract: Background: Obsessive-compulsive disorder (OCD) is a psychiatric disorder marked by obsessive thoughts and repetitive actions, driven by genetic and environmental factors. Altered brain circuits, notably hyperactivity in the orbitofrontal cortex and striatum, are implicated. The underlying molecular mechanisms that produce these alterations are, however, not well understood. Genetic studies have begun to identify major risk genes related to OCD, with a significant focus on Slitrk5, a TrkB co-receptor, involved in synapse formation and neurotrophic signaling as well as glutamate transmission and neuronal excitability. Recent findings also indicate a complex interaction between TrkB and mGluR5 receptors, suggesting a novel mechanism by which neurotrophic signaling can affect glutamate transmission and neuronal excitability. These findings highlight the critical role of glutamate signaling and neuronal plasticity in understanding the molecular mechanisms underlying OCD symptoms and the potential bridging role of Slitrk5.
Aim: We aim to elucidate Slitrk5's role in synaptic transmission, impacting neurotrophic and glutamatergic signaling, potentially underlying cortical hyperactivity in OCD.
Methods: Using both human cell lines and cultured primary mouse neurons, we use a combination of targeted and unbiased approaches. We adopt functional and biochemical assays in association with genetic and pharmacological perturbations to determine the molecular action mechanism of Slitrk5 in response to brain-derived neurotrophic factor (BDNF). In parallel, we carry out a Slitrk5 interactome analysis through which we identify key players involved in the

BDNF-TrkB-Slitrk5 signaling pathways as well as expand the repertoire of potential treatment targets for next generation OCD treatments.
Results: We generated a stable Slitrk5 expressing 293HEK line to have a suitable model to investigate the function and trafficking of this TrkB co-receptor at baseline and in response to BDNF. In line with previous literature, we found that Slitrk5 perturbs the BDNF-induced TrkB pathway via calcium imaging. Ongoing interactome analyses will further elucidate the kinetic and signaling dynamic.
Conclusions: This study will help elucidate how the OCD-related gene Slitrk5 influences neurotrophic signaling pathways and glutamatergic transmission, potentially explaining cortical hyperactivity in OCD. Additionally, identified interactors from proteomics may uncover new key players underlying OCD mechanisms and new potential treatment targets for OCD-symptom-specific treatments.

Disclosures: S. Martinelli: None. **F.S. Lee:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.07/B58

Topic: B.04. Synaptic Transmission

Support: R01 MH126929
U24 DK116195
Stanfrd MCHRI 1220319-117-JHACT
Swiss National Science Foundation SNSF 211053

Title: Alternative splicing of latrophilin-3 controls synapse formation

Authors: *S. WANG;
Stanford Univ., Stanford, CA

Abstract: The assembly and specifcation of synapses in the brain is incompletely understood. Latrophilin-3 (Lphn3)—a postsynaptic adhesion G-protein-coupled receptor—mediates synapse formation in the hippocampus but the mechanisms involved remain unclear. Here we show in mice that LPHN3 organizes synapses through a convergent dual-pathway mechanism: activation of Gαs signalling and recruitment of phase-separated postsynaptic protein scafolds. We found that cell-type-specifc alternative splicing of Lphn3 controls the LPHN3 G-protein-coupling mode, resulting in LPHN3 variants that predominantly signal through Gαs or Gα12/13. CRISPR-mediated manipulation of Lphn3 alternative splicing that shifts LPHN3 from a Gαs- to a Gα12/13-coupled mode impaired synaptic connectivity as severely as the overall deletion of Lphn3, suggesting that Gαs signalling by LPHN3 splice variants mediates synapse formation. Notably, Gαs-coupled, but not Gα12/13-coupled, splice variants of LPHN3 also recruit phase-transitioned postsynaptic protein scafold condensates, such that these condensates are clustered

by binding of presynaptic teneurin and FLRT ligands to LPHN3. Moreover, neuronal activity promotes alternative splicing of the synaptogenic Gαs-coupled variant of LPHN3. Together, these data suggest that activity-dependent alternative splicing of a key synaptic adhesion molecule controls synapse formation by parallel activation of two convergent pathways: Gαs signalling and clustered phase separation of postsynaptic protein scafolds.

Disclosures: S. Wang: None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.08/B59

Topic: B.04. Synaptic Transmission

Support: 1ZIANS003140-08

Title: Examining the subcellular localization of the intracellular domain of neuroligins

Authors: *T. H. DO, K. MCDANIEL, K. W. ROCHE;
NIH, Bethesda, MD

Abstract: Neuroligins (NLGNs) are a family of transmembrane synaptic adhesion molecules located at the post-synapse that are important for synapse formation and function. Humans have five isoforms: NLGN1-3, 4X, and 4Y. All NLGNs are regulated by post-translational modifications, such as through isoform-specific phosphorylation. Additionally, NLGNs undergo proteolytic cleavage (Venkatesh et al., 2015, Suzuki et al., 2012, Peixoto et al., 2012). For example, work from our group has identified unique activity-dependent regulation of NLGN3 cleavage. Cleavage of NLGN3 results in an extracellular domain (ECD) and cellular C-terminal fragments (CTFs). While work has been done on the ECD of NLGN3 in the context of glioma, the physiological function of all NLGN CTFs remains unknown. We are investigating the subcellular localization of the NLGN family intracellular domains (ICDs) post-cleavage. To begin characterizing the NLGN CTFs, we generated truncation constructs: 1) NLGN with only the transmembrane and intracellular domains (termed TMD) and 2) exclusively the NLGN ICD. Using immunoblots, we tested the expression of these truncated proteins in HEK293T cells following PMA treatment to induce cleavage. With the full-length protein, we found that NLGN3 undergoes robust cleavage, NLGN1 undergoes minimal cleavage, and NLGN2 does not undergo cleavage. The TMD and ICD truncations of all three NLGNs were not affected by PMA treatment, demonstrating that the extracellular domain of these proteins is required for PMA induced cleavage. To examine the localization of these truncations, we transfected the truncated constructs in HeLa cells and performed immunocytochemistry. Our preliminary results show that the NLGN3 ICD localizes to the nucleus compared to the full-length protein. These results provide critical insight into the physiological role of NLGN proteolytic cleavage and establish isoform-specific effects.

Disclosures: T.H. Do: None. **K. McDaniel:** None. **K.W. Roche:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.09/B60

Topic: B.04. Synaptic Transmission

Support: DFG 232550447

Title: Molecular basis of the cytoskeletal anchoring of gephyrin

Authors: *P. LORENZ[1], A. PACIOS MICHELENA[1], C. WERNER[2], C. VILLMANN[3], H. SCHINDELIN[1];
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Abstract: Gephyrin is a 93 kDa-scaffolding protein which ensures the anchoring, clustering and stabilization of glycine and $GABA_A$ receptors (GlyRs and $GABA_A$Rs, respectively) at inhibitory synapses. Furthermore, gephyrin interacts with elements of the cytoskeleton including the actin-organizing proteins of the ena/VASP family, which includes mena, EVL and VASP. Ena/VASP proteins regulate actin dynamics and thus play a role in neurulation, neuronal migration, dendritic morphology and synapse formation. As the physiological role of the ena/VASP association with gephyrin is still poorly defined, we want to elucidate the importance of this interaction for the formation, maintenance and functionality of inhihibory postsynapses. First, we studied the complex formation between gephyrin and VASP using analytical size exclusion chromatography, native gel electrophoresis and microscale thermophoresis. The respective binding sites in gephyrin and in VASP were mapped. To understand the relevance of the gephyrin-ena/VASP interaction we performed colocalization studies based on structured illumination microscopy. Previous studies demonstrated significant colocalization of gephyrin and mena/VASP at synaptic sites in murine hippocampal and cortical neurons. The newly acquired results indicate that the localization of mena is significantly more correlated with gephyrin than with actin, while additionally showing numerous extrasynaptic signals. To elucidate the importance of the ena/VASP association with gephyrin for the formation and maintenance of inhibitory postsynapses we measured the size and number of gephyrin-$GABA_A$R clusters in the absence of ena/VASP using immunocytochemistry studies in NSC-34 cells. In the absence of mena and VASP, the overall cluster number/cell as well as the mean gephyrin fluorescence were significantly reduced compared to untransfected cells. In addition, gephyrin clusters were significantly smaller. These studies provide molecular insights into the physiological relevance of the interaction between gephyrin and ena/VASP proteins underlining its potential importance for the functionality of inhibitory postsynapses.

Disclosures: P. Lorenz: None. **A. Pacios Michelena:** None. **C. Werner:** None. **C. Villmann:** None. **H. Schindelin:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.10/B61

Topic: B.04. Synaptic Transmission

Support: NINDS intramural funds

Title: Cryo-em tomography and automatic segmentation-assisted characterization of postsynaptic density isolated from rat cerebral cortex

Authors: *J. JUNG[1], E. CHOI[2], X. CHEN[3], T. S. REESE[4];
[1]Natl. Inst. of Hlth., Bethesda, MD; [2]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [3]Lab. of Neurobio., NINDS, Bethesda, MD; [4]NINDS, NIH/ NINDS, Bethesda, MD

Abstract: Postsynaptic densities (PSDs) are large protein complexes associated with the postsynaptic membrane of excitatory synapses. They contain proteins essential for synaptic function including plasticity. Electron microscopy (EM) has been used to study PSDs, typically depicting PSDs as compact disk-like structures of hundreds of nanometers in size; studies on biochemically isolated PSDs revealed several key PSD proteins and showed the presence of PSDs structurally similar to typically depicted PSDs. In our previous study, isolated PSD fractions were sonicated to break weakly bound structures within PSDs revealing PSD fragments (40 - 90 nm in size) separate from the typical PSDs based on 2D EM images; in our recent study, two isolated PSDs after sonication were visualized in 3D by cryo-EM tomography exhibiting their irregular contours with granular or modular substructures and also showing that a considerable portion of the substructures are similar to those PSD fragments in size. Using our automatic segmentation approach enabling the segmentation of the substructures within the PSDs, here we examined more isolated PSDs after sonication to determine if all the PSDs contain the same substructures similar to those PSD fragments. Indeed, we found those substructures among all the newly examined PSDs, and the portion of the substructures was more than 40% indicating that the substructures are commonly present among the PSDs. We also found large substructures more than 90 nm that can potentially span the entire thickness of a typical flat-disk shaped PSD. Our findings here are consistent with our previous studies further supporting that the modular nature of the PSD facilitates remodeling of the PSD for proper synaptic function and plasticity.

Disclosures: J. Jung: None. **E. Choi:** None. **X. Chen:** None. **T.S. Reese:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.11/B62

Topic: B.04. Synaptic Transmission

Support: 1ZIANS003140-08

Title: Intracellular signaling of neuroligin-3 post-cleavage

Authors: *K. F. MCDANIEL, T. H. DO, K. W. ROCHE;
Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: Synapse formation is crucial to proper neurodevelopment and refinement of neural circuits throughout life. Neuroligins (NLGNs) are a family of post-synaptic adhesion molecules that are vital for the maintenance and function of synapses. NLGN3, an X-chromosome linked protein, is the only NLGN to localize to both excitatory and inhibitory synapses. Previously, our lab and others have found that NLGN3 can be cleaved just upstream of the transmembrane domain, creating a soluble ectodomain (ECD). Cleavage can occur in basal and active states and the soluble ECD has been found to be a potent glioma mitogen. While the ECD of NLGN3 has been studied, the C-terminal fragments (CTFs) that remain in the cell have yet to be investigated. We aim to characterize the CTF(s) and their physiological intracellular role, including signaling pathways and localization. Here, we report multiple CTF species, differentiated by size on immunoblots, that are stable for at least 60 minutes in culture. Using the well-established signaling pathway of Notch as a model, we have found that truncations of NLGN3 that contain only the intracellular domain localize to the nucleus of both heterologous cells and primary hippocampal neurons in culture. Additionally, with immunocytochemistry, we have found that the CTF(s), following full-length NLGN3 cleavage, also localize to the nucleus. Further experiments include additional characterization of the NLGN3 nuclear fragment and the downstream signaling implications of this localization. This work establishes a previously unknown role of NLGN3 cleavage and localization to the nucleus and broadens our understanding of the physiological role of synaptic adhesion molecules.

Disclosures: K.F. McDaniel: None. **T.H. Do:** None. **K.W. Roche:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.12/B64

Topic: B.04. Synaptic Transmission

Title: Spinophilin and Neurabin: Examining Biochemical and Functional Divergence in Homologous Synaptic Scaffolding Proteins

Authors: *N. SHAH[1], W. COREY[2], A. J. BAUCUM II[3];
[1]Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Pharmacol. and Toxicology, Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Motor learning is facilitated by the striatum and the coordinated action of its two principal cell types: direct and indirect medium spiny neurons (MSNs). The organization of protein complexes within the post-synaptic density (PSD) of striatal MSNs regulates MSN activity and striatal circuit function. Spinophilin and neurabin are PSD-enriched, homologous, protein phosphatase 1 (PP1) targeting proteins. Despite considerable structural and functional overlap, global knockout (KO) studies demonstrate unique roles for these two proteins. Our previous studies found spinophilin KO (Spino-/-) mice had decreased rotarod motor learning in a 5-day, 3-trial per day paradigm. In contrast, neurabin KO (Nrb-/-) mice outperformed the WT comparison group in both a 5-day and 8-day paradigm. Both Spino-/- and Nrb-/- mice had a trend for an increased reversal behavior on the rotarod, a previously reported index of impaired action selection. Preliminary data suggest that mice lacking neurabin specifically in direct pathway medium spiny neurons (dMSNs; NrbΔdMSN) had an increased latency to fall and demonstrate increased reversal behavior. Using immunoblotting, we also found that rotarod motor learning impacts synaptic protein expression, as we observed increased levels of striatal neurabin, but not spinophilin, and increased levels of spinophilin and neurabin-targeted substrates: Homer1, PP1 alpha, PP1 gamma, GluA1, and GluA2. Spinophilin and neurabin target PP1 to overlapping substrates, and accordingly, we found largely overlapping distribution of spinophilin and neurabin mRNA within the cortex, striatum, cerebellum, and olfactory bulb. However, there was greater distribution of neurabin transcripts in brain stem and spinophilin transcripts in the thalamus. Moreover, spinophilin mRNA was enriched in puncta within the neuropil compared to nuclear localization of neurabin mRNA, consistent with the known local, dendritic spine translation of spinophilin compared with neurabin. These studies delineate unique contributions of spinophilin and neurabin to striatal circuit function and PSD biochemistry, while suggesting unique regulation or actions by which they may do so.

Disclosures: N. Shah: None. **W. Corey:** None. **A.J. Baucum II:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.13/B65

Topic: B.04. Synaptic Transmission

Title: The role of allopregnanolone in $GABA_A$ receptor neuroadaptations in mice

Authors: *S. SHEPARD[1], W. HAN[2];
[1]NIH/ NINDS, Bethesda, MD; [2]NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD

Abstract: Allopregnanolone (ALLO), a reduced metabolite of progesterone, is an endogenous neuroactive steroid produced in the central nervous system. Reduced ALLO levels have been linked to various psychiatric disorders such as major depressive disorder, post-partum depression, and anxiety disorders. Traditionally selective serotonin reuptake inhibitors (SSRIs) served as the common antidepressants; however, recently brexanolone, a synthetic preparation of ALLO, was approved by the Food and Drug Administration (FDA) to specifically treat post-partum depression. ALLO acts as a positive allosteric modulator of the γ-aminobutyric acid type A receptors ($GABA_ARs$). Here, we have investigated inhibitory synaptic neuroadaptations after acute and chronic treatments of a sedative dose of ALLO using biochemical methods. We hope to provide deeper insight into the novel molecular mechanisms and pharmacological effects of ALLO treatment in GABAergic synapses in mice.

Disclosures: S. Shepard: None. **W. Han:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.14/B66

Topic: B.04. Synaptic Transmission

Support: JSPS KAKENHI JP22K06428

Title: Possible roles of tubulin in the postsynaptic density

Authors: *T. SUZUKI[1], T. FUJII[2], K. KAMETANI[1], W. LI[3], K. TABUCHI[4];
[1]Shinshu Univ., Matsumoto, Japan; [2]Shinshu Univ. Textile Sci. & Technol., Ueda, Japan; [3]Shanghai Jiao Tong Univ., Shanghai, China; [4]Mol. & Cell. Physiol., Shinshu Univ. Academic Assembly, Matsumoto, Japan

Abstract: The presence and roles of tubulin in and around the postsynaptic density (PSD) has long been a point of debate, despite the identification of tubulin immunoreactivity in the PSD as early as 1975. In our previous paper (Suzuki et al., 2021, *Life Science Alliance*, 4; e202000945) we suggested a fundamental role for tubulin in the structure of the postsynaptic density (PSD) at excitatory synapses based on our experiments on PSD lattice (PSDL), which is supposed to be a backbone structure for PSD. This investigation extends our prior exploration of the PSDL. We investigated the interaction of PSD and PSDL with growing microtubules. Interactions between PSDL/PSD structures and growing microtubules were observed at the electron microscopy level. This study supports the previous finding that the PSD traps transiently invading microtubules during synaptic plasticity expression. We identified PSDL-like meshwork structures and their connection to microtubules in the purified tubulin sample (purity, >99%). This result suggests the possibility that PSDL structure is constructed by tubulin alone. Furthermore, we found unique dysintegration of PSDL and PSD structures. The details of this decomposition will be provided in the meeting and discussed. These results strengthen the idea that tubulin is a

fundamental building block of PSD architecture and that tubulin has the potential to form unique structures distinct from traditional microtubules in the postsynaptic region. In summary, this investigation suggests the involvement of tubulin in the PSD and PSDL in the construction and function (interaction with growing microtubules) of PSD.

Disclosures: T. Suzuki: None. **T. Fujii:** None. **K. kametani:** None. **W. Li:** None. **K. Tabuchi:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.15/B67

Topic: B.04. Synaptic Transmission

Title: Characterisation of MAGI proteins in human iPSC-derived neurons

Authors: M. BORGMEYER, T. FANUTZA, D. LAU, C. WOZNY, ***N. WITTENMAYER**; Fac. of Med., Med. Sch. Hamburg, Hamburg, Germany

Abstract: Synapse formation is critical for the wiring of neural circuits in the developing brain. The composition and function of synapses has predominantly been studied in rodent cells. Here we show a novel protocol to generate human iPSC-derived forebrain-like neurons that show rapid synaptic development. To achieve this, we use an astrocyte feeder layer attached to a complex mix of ECM-components. Neuronal stem cells (NCS) are plated on this layer for maturation into neurons. We use this protocol to provide an initial characterisation of MAGI proteins in human neurons. Both MAGI-1 and MAGI-2 are expressed in the brain, however expression levels of MAGI-2 are much higher in neurons than in any other cell type, while MAGI-1 is expressed more evenly throughout cell types and tissues. In rodents the synaptic scaffolding protein S-SCAM/MAGI-2 plays a critical role in the assembly and maintenance of synapses and interacts with signalling proteins facilitating synapse to nucleus signalling. Increased expression of S-SCAM/MAGI-2 in the human brain is associated with schizophrenia. Here, we show that MAGI-1 can be found at both inhibitory and excitatory synapses in human neurons and can substitute for the loss of MAGI-2 during the multicomponent process of synapse formation.

Disclosures: M. Borgmeyer: None. **T. Fanutza:** None. **D. Lau:** None. **C. Wozny:** None. **N. Wittenmayer:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.16/B68

Topic: B.04. Synaptic Transmission

Support: NIH Grant 1ZIANS003140-10

Title: A New NLGN4X Variant Cluster in Autism Spectrum Disorder

Authors: *E. HONG[1], ***E. HONG**[2], M. J. HENDERSON[3], W. YE[3], J. MARUGAN[3], W. LU[1], K. W. ROCHE[1];
[1]NINDS, NIH, Bethesda, MD; [2]NIH/ NINDS, Bethesda, MD; [3]NCATS, NIH, Rockville, MD

Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties in social interactions, deficits in communication, and repetitive behaviors. Numerous genes have been identified as potential contributors to ASD based on both human genetics and etiological evidence. Among these genes, neuroligins (NLGN1-3, NLGN4X, and NLGN4Y) have emerged as strongly linked to ASD. NLGNs are postsynaptic cell adhesion molecules that interact with presynaptic neurexins (NRXNs) and play a crucial role in neuronal development, synaptic transmission, and synaptic plasticity. Within the NLGN family, NLGN4X stands out with the highest number of variants associated with ASD. Most of these rare variants are located within the extracellular esterase homology domain, and these mutations lead to issues with surface expression and impaired neuronal function. Notably, multiple variants within the first 100 amino acids of NLGN4X (Nguyen et al., Neuron, 2020) display trafficking defects. We have now identified a new cluster of variants slightly downstream (aa 235-245) from the previously characterized cluster. These new variants lead to severe trafficking defects in NLGN4X. Analysis of the crystal structure reveals that each of these variants is likely to disrupt the overall structure, leading to significant steric clashes with surrounding residues. Through extensive biochemical and imaging studies, we find that these variants exhibit impairments in protein trafficking, surface expression, and synaptogenesis. We also conducted library screens in collaboration with the National Center for Advancing Translational Sciences (NCATS), and we are currently validating several drug candidates that rescue trafficking deficits across multiple assays. This discovery sheds light on the structure/function relationship of ASD variants and provides valuable insights into potential therapeutic targets for individuals affected by this condition.

Disclosures: E. Hong: None. **E. Hong:** None. **M.J. Henderson:** None. **W. Ye:** None. **J. Marugan:** None. **W. Lu:** None. **K.W. Roche:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.17/B69

Topic: B.04. Synaptic Transmission

Support: R37MH080046
R01MH119826

Title: Dissecting the functional properties of single glutamatergic synapses with optical physiology

Authors: *S. T. BARLOW[1], T. A. BLANPIED[2];
[1]Dept. of Physiol., Univ. of Maryland Baltimore, Baltimore, MD; [2]Dept. of Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Fluorescent sensors for glutamate release and postsynaptic calcium signaling are promising tools for answering fundamental questions about synaptic physiology at individual glutamatergic synapses. However, leveraging these optical tools for synaptic neuroscience requires scalable experimental frameworks. We devised a high-throughput approach that efficiently collects and analyzes hundreds of optical recordings of stimulus-evoked or spontaneous glutamate release activity across the axonal arbors of cultured rat hippocampal neurons using the third-generation glutamate fluorescent reporter, iGluSnFR3.
With iGluSnFR3, we tracked the function of single, putative boutons in response to single stimuli. We found that iGluSnFR3 possessed excellent spatial specificity for single boutons, allowing us to differentiate the physiology of boutons separated by <3 µm. We observed remarkable heterogeneity in the magnitude and variation of glutamate release across various Ca^{2+} concentrations, implying that boutons across single axonal arbors possessed distinct organizations of their vesicle release machinery. This motif was more obvious when we stimulated neurons with paired stimuli, where we were able to observe diverse short-term plasticity behavior across boutons. Intriguingly, boutons did not exhibit uniform facilitation curves across interstimulus intervals, with boutons instead preferentially facilitating at certain interstimulus intervals - these unique time constants for facilitation at different boutons once again support the notion that heterogeneous organization of the presynaptic terminal drives distinct presynaptic computational properties.
Finally, we deployed iGluSnFR3 together with a spine-localized Ca^{2+} sensor, which enabled all-optical measurement of NMDA receptor (NMDAR)-mediated, spontaneous synaptic transmission at individual dendritic spines. On dendritic spines with two synaptic contacts, we observed spatially discrete NMDAR signaling, with minimal synaptic spillover. This assay lays the groundwork for the direct assessment of NMDAR activation at the level of individual synapses. Together with post-hoc immunocytochemistry and/or super-resolution imaging of synaptic proteins, these assays will provide detailed structure-function analyses of single synapses.

Disclosures: S.T. Barlow: None. **T.A. Blanpied:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.18/B70

Topic: B.04. Synaptic Transmission

Support: NIH Grant EY012141
NIH Grant EY032506
Research to Prevent Blindness International Travel Award

Title: Using MINFLUX microscopy to probe nanoscopic receptor organization of the mammalian cone photoreceptor synapse

Authors: *S. DEVRIES[1], D. FUTAGI[2];
[1]Ophthalmology, Northwestern Univ., Chicago, IL; [2]Ophthalmology, Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Unlike central synapses where the pre- and postsynaptic elements are opposed across a 20 nm cleft, the cone synapse has a tiered organization where the dendrites of different bipolar cell types terminate progressively further from ribbon active zones up to ~1 µm. Superresolution microscopy shows that central synapses have a nanocolumnar organization that promotes efficient transmission. A similar nanocolumnar organization and efficiency considerations are unlikely to apply at the cone synapse due to its spatially extended geometry. Here, we use MINFLUX microscopy, which can localize individual fluorophores to 2-3 nm in 3D, to test the hypothesis that receptor density decreases with distance from vesicle fusion sites. Retinal whole-mounts from the cone-dominant ground squirrel were fixed in 2% glyoxal, agar embedded, and sliced tangentially with a vibratome at the level of the cone terminals. Sections were labeled with antibodies to ribeye (ctbp2), bassoon, GluA4, elfn2, mgluR6, and GluK1. Secondary antibodies were visualized with DNA paint exchange. Z-slice (~800 nm) images were acquired with an Abberior MINFLUX microscope. Postprocessing consisted of calculating the centroid location of the fluorphore from 5-100 repeat localizations during a “blink”. In MINFLUX sections, antibodies to both ribeye and bassoon labeled thin crescent-shaped structures ~100-300 nm in length. Prominent, elongated aggregates of GluA4-containing AMPA receptors ran parallel to ribeye at distances of 190.8±29.6 nm (LDA, Linear discriminant analysis, mean±SD; n=27 pairs, 2 cones) and were coplanar as demonstrated by PCA (91.7-98.1% of the features were captured in 2D plots). mGluR6 and elfn2 were colocalized with a peak nearest-neighbor distance of ~50 nm, consistent with adjacency. Both mGluR6 and elfn2 were less compactly organized by visual inspection relative to GluA4. GluK1 labeling was the most distant from ribeye and widely distributed with little discernible substructure. Information entropy measurements following KDE showed that GluA4 was significantly more organized (10.72±1.38 bits, n=3) than either mGluR6/elfn2 (13.68±0.44 bits, n=5;p=0.0036 vs GluA4) and GluK1 (14.35±0.75 bits, n=4; p=0.0061 vs GluA4). While mGluR6/elfn2 was more organized than GluK1, the difference was just below statistical significance. The distributions may reflect energetic trade-offs between epsc amplitude, receptor number, and distance from release sites.

Disclosures: S. DeVries: None. **D. Futagi:** None.

Poster

PSTR439: Transsynaptic Organization and Structure

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR439.19/B71

Topic: B.04. Synaptic Transmission

Support: NINDS and NIBIB intramural research programs.

Title: Postsynaptic organization of endogenous PSD-95 corresponds to presynaptic priming/fusing vesicles in glutamatergic excitatory synapses

Authors: *X. CHEN[1], C. A. WINTERS[1], A. JAN[3], M. ARONOVA[4], V. T. CROCKER[2], S. MOREIRA[2], R. D. LEAPMAN[5], T. S. REESE[6];
[1]Lab. of Neurobio., [2]NINDS EM facility, NINDS/NIH, Bethesda, MD; [3]Dept. of Behavioral Hlth., Henry Ford Hosp., Detroit, MI; [4]Lab. of Cell. Imaging and Macromolecular Biophysics, Natl. Inst. of Biomed. Imaging and Bioengineering, Natl. Inst. of Healt, Bethesda, MD; [5]Natl. Inst. of Biomed. Imaging & Bioengineering, NIH, Bethesda, MD; [6]NINDS, NIH/ NINDS, Bethesda, MD

Abstract: PSD-95 and its family members are major scaffolding proteins located in the postsynaptic density (PSD) in the excitatory glutamatergic synapses. By interacting with host of PSD proteins, such as main glutamate receptors and their associates, and with adhesion molecules spanning synaptic cleft, PSD-95 is well positioned to play pivotal roles in the overall molecular organization of the PSD. Consistent with this notion, immunogold labeling of PSD-95 on isolated PSDs from the brain demonstrated its prevalent distribution across the PSD**,** furthermore, estimate of the copy number of PSD-95 per PSD matches the number of vertical filaments in the core structure of the intact PSDs illustrated by EM tomography; knocking down PSD-95, or knocking down PSD-95 and its family members altogether markedly reduced the PSD areas. In recent years, super resolution light microscopy imaging has made great strides in illuminating organization of synaptic proteins, one of the findings is that PSD-95 along with AMPARs exist in ~ 100 nm subsynaptic nanoclusters or nanodomains at synapses, and PSD-95 nanocluster aligns with presynaptic active zone protein RIM. To more definitively understand endogenous PSD-95 organization in the PSD, here we used dark field scanning transmission EM (STEM) tomography to reconstruct glutamatergic excitatory synapses immunolabelled by either PSD-95 intrabodies or antibody, our results are indicative of more prevalent PSD-95 distribution across the PSD rather than in tight nanoclusters, and PSD-95 labels are all essentially corresponding with high fidelity to priming/fusing vehicles attaching to the presynaptic terminals, demonstrating directly that PSD-95 is part of the important transsynaptic molecular machineries linking the presynaptic vesicle fusing protein complexes to key molecular constitutes across the PSD.
Supported by the NINDS, NIBIB intramural research programs, we thank Susan Cheng of NINDS EM facility for providing the EM block of the PSD-95 immunogold labeled mouse brain sample.

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Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.01/B72

Topic: B.04. Synaptic Transmission

Support: NIH Intramural Research Program

Title: The TMEM132B-GABAA receptor complex controls alcohol actions in the brain

Authors: *G. WANG[1], S. PENG[2], W. HAN[2], D. CASTELLANO[3], L. DONG[4], W. LU[5]; [1]Natl. Inst. of Hlth., NINDS, Bethesda, MD; [2]NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD; [3]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [4]Natl. Inst. of Hlth., NEI, Bethesda, MD; [5]NINDS/NIH, Bethesda, MD

Abstract: Alcohol is the most consumed and abused psychoactive drug globally, but the molecular mechanisms driving alcohol action and its associated behaviors in the brain remain enigmatic. Here we have discovered a transmembrane protein TMEM132B that is a GABAA receptor (GABAAR) auxiliary subunit. Functionally, TMEM132B promotes GABAAR expression at the cell surface, slows receptor deactivation, and enhances allosteric effects of alcohol on the receptor. In TMEM132B knockout (KO) mice or TMEM132B I499A knockin (KI) mice in which the TMEM132B-GABAAR interaction is specifically abolished, GABAergic transmission is decreased and alcohol-induced potentiation of GABAAR-mediated currents is diminished in hippocampal neurons. Behaviorally, anxiolytic and sedative/hypnotic effects of alcohol are markedly reduced, and compulsive, binge-like alcohol consumption is significantly increased in TMEM132B KO or KI mice. Taken together, these data reveal a new GABAAR auxiliary subunit, identify the TMEM132B-GABAAR complex as a major alcohol target in the brain, and provide critical mechanistic insights into alcohol-related behaviors

Disclosures: G. Wang: None. **S. Peng:** None. **W. Han:** None. **D. Castellano:** None. **L. Dong:** None. **W. Lu:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.02/B73

Topic: B.04. Synaptic Transmission

Support: Palm Health-Sponsored Program in Computational Brain Science and Health

Title: Interleaved single and bursting spiking resonance

Authors: C. C. CEBALLOS[1], E. LOWET[2], ***R. PENA**[1];
[1]Biol. Sci., Florida Atlantic Univ., Jupiter, FL; [2]Erasmus Univ. in Rotterdam, Rotterdam, Netherlands

Abstract: Under *in vivo* conditions, CA1 pyramidal cells from the hippocampus display transitions from single spikes to bursts. It is believed that subthreshold hyperpolarization and depolarization, also known as down and up-states, play a pivotal role in these transitions. Nevertheless, a central impediment to correlating suprathreshold (spiking) and subthreshold activity has been the technical difficulties of this type of recording, even with widely used calcium imaging or multielectrode recordings. Recent works using voltage imaging have been able to correlate spiking patterns with subthreshold activity in a variety of CA1 neurons, and recent computational models have been able to capture these transitions. In this work, we used a computational model of a CA1 pyramidal cell to investigate the role of intrinsic conductances and oscillatory patterns in generating down and up-states and their modulation in the transition from single spiking to bursting. Specifically, the emergence of distinct spiking resonances between these two spiking modes that share the same voltage traces in the presence of theta or gamma oscillatory inputs, a phenomenon we call interleaved single and bursting spiking resonance. We noticed that these resonances do not necessarily overlap in frequency or amplitude, underscoring their relevance for providing flexibility to neural processing. We studied the conductance values of three of the main subthreshold activated (resonant or amplifying) currents in our model: persistent sodium current (I_{NaP}) and its conductance G_{NaP}, delayed rectifier potassium (I_{KDR}) and its conductance G_{KDR}, and hyperpolarization-activated current (I_h) and its conductance G_h. The expression of the different channels likely varies across CA1 and hippocampus, so it is important to systematically modify their conductances. We noticed that G_{NaP} and G_{KDR} have opposite effects in generating bursts and in their resonance effects and that they modulate the phase-locking. Surprisingly, G_h can only slightly affect the interleaved resonance. Our results point out the relevance of the precise expression of these three conductances to facilitate the transmission of single spikes and bursts and their resonances, which are essential for the emergence of *in vivo* states. Acknowledgments: This work was supported by the Palm Health-Sponsored Program in Computational Brain Science and Health and the FAU Stiles-Nicholson Brain Institute. The authors declare that they have no conflict of interest.

Disclosures: C.C. Ceballos: None. **E. Lowet:** None. **R. Pena:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.03/B74

Topic: B.04. Synaptic Transmission

Title: Differential effects of ethanol on excitatory and inhibitory synaptic transmission in visual cortex of wild-type and adenosine A_1R knock-out mice

Authors: *N. L. RAFFONE[1], M. CHISTYAKOVA[1], M. A. VOLGUSHEV[1,2];
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Abstract: Ethanol is one of the most commonly used substances in the world. While the behavioral effects of ethanol are well characterized, mechanisms of its action on neurons and synapses remain elusive. Knowledge of ethanol's effects on synaptic transmission is paramount for understanding its effects on cognitive functions. Prior research suggests that ethanol has heterogeneous effects on excitatory and inhibitory transmission across different brain regions studied in different species. Possible dependence on brain region and species prevents simple transfer of results. Getting a complete picture of ethanol's action on the brain necessitates the study of each brain region. Prior research has also suggested that ethanol could affect neurons by interfering with metabolism of biologically active molecules, such as adenosine. Previous work in rats from our lab showed that excitatory transmission was consistently suppressed by increasing levels of ethanol. Blocking adenosine A_1 receptors (A_1R) with the selective antagonist DPCPX (8-cyclopentyl-1,3-dipropylxanthine) attenuated ethanol's effects at low concentrations (1-10 mM) but not at high concentrations (50 mM) suggesting an adenosine-dependent pathway at low concentrations and an adenosine-independent pathway at high concentrations (Luong *et al.,* 2017). Here, we explored the involvement of A_1Rs in mediating ethanol's effects on synaptic transmission to layer 2/3 pyramidal neurons of visual cortex using wild type (WT) and A_1R knock-out (KO) mice. Ethanol differentially affected excitatory and inhibitory transmission in WT and KO mice. In slices from WT mice ethanol had heterogeneous effects on excitatory transmission (facilitation, suppression or no change), with no net change. Ethanol's effects remained heterogeneous during acute blockade of A_1Rs with DPCPX. However, in A_1RKO mice ethanol consistently suppressed excitatory transmission with no cases of enhancement. Inhibitory transmission was suppressed by ethanol in both WT and A_1RKO mice. At both excitatory and inhibitory synapses, changes of response amplitude correlated with changes of paired-pulse ratio suggesting involvement of presynaptic mechanisms. We conclude that A_1Rs are not involved in mediating effects of ethanol on synaptic transmission in mouse visual cortex. However, A_1Rs are necessary for development of mechanisms mediating facilitation at some excitatory synapses. Our results add evidence for the diversity of ethanol's effects and mechanisms of action on synaptic transmission in different brain structures, and even in the same brain area (visual cortex) in different species, rats vs. mice.

Disclosures: N.L. Raffone: None. **M. Chistyakova:** None. **M.A. Volgushev:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.04/B75

Topic: B.04. Synaptic Transmission

Support: NIH Grant R00 MH110665

Title: Kit Ligand Acutely Modulates the Inhibition of Purkinje Cells

Authors: *M. R. WILLIAMS[1], T. ZAMAN[2];
[1]Pediatrics & Human Develop., Michigan State Univ., Grand Rapids, MI; [2]Pediatrics & Human Develop., Michigan State Univesity, Grand Rapids, MI

Abstract: The proto-oncogene Kit receptor tyrosine kinase is enriched in discrete populations of neurons throughout the mammalian brain. Mutation of Kit is affiliated with rare cases of neurological abnormalities and neurodevelopmental disorders. We have recently demonstrated in mice that developmental knockout of Kit from Molecular Layer Interneurons of the cerebellar cortex reduces GABAergic inhibition to Purkinje cells. A similar phenotype was observed when the transmembrane protein Kit Ligand (KL) was depleted from Purkinje cells, regardless of whether KL knockout occurred developmentally or in adulthood. This finding suggested that KL mediated Kit kinase activity may modulate of MLI-PC inhibition throughout the lifespan. To determine if acute manipulations in KL-Kit signaling alter MLI-PC inhibition, we investigated the effects of exogenous KL in acute slices of the mouse cerebellum. We found that applying a commercially available recombinant form of the extracellular soluble domain of KL produced a potentiation of inhibition to PCs. This effect was observed either after 30 minute bath application or 5 minute perfusion. The KL mediated potentiation of inhibition was not observed in slices derived from animals lacking cerebellar expression of Kit receptor. MLI types include MLI-1, which directly inhibit PCs, and MLI-2 which inhibit MLI-1s. We are in the process of determining whether KL mediated enhancement of PC inhibition may occur through potentiation of MLI-1 mediated PC inhibition, or through reduced MLI-2 mediated inhibition of MLI-1s. We do not yet exclude the possibility that KL stimulates less well understood sources of PC inhibition, such as PC collaterals, and PC layer interneurons. Revealing the cell and circuit mechanisms of PC inhibition will ultimately inform the basis of cerebellar dependent learning, behavior, and non-motor functions. Furthermore, elucidating the mechanisms of KL-Kit in adult synapse biology may introduce new pathways of synaptic plasticity relevant to the other circuits in which these gene products are expressed.

Disclosures: M.R. Williams: None. **T. Zaman:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.05/B76

Topic: B.04. Synaptic Transmission

Support: NIH Grant 1ZIAHD001205-31

Title: Opioids potentiate medial habenula cholinergic afferent input onto interpeduncular nucleus GABAergic neurons

Authors: *R. CHITTAJALLU[1], A. VLACHOS[2], X. YUAN[3], S. HUNT[1], E. LONDON[4], K. A. PELKEY[5], C. J. MCBAIN[6];
[1]NICHD, NIH, Bethesda, MD; [2]Eunice Kennedy Shriver Natl. Inst. of Child Hlth. an, Rockville, MD; [3]NIH, Bethesda, MD; [4]Eunice Kennedy Shriver Natl. Inst. of Child Hlth. an, Bethesda, MD; [5]NICHD/LCSN, NIH, Silver Spring, MD; [6]Lab. Cell/Molec Neurosci, NIH, Bethesda, MD

Abstract: The medial habenula (mHb)/interpeduncular nucleus (IPN) axes, termed the dorsal diencephalic conduction system (DDC), is anatomically positioned to receive incoming forebrain signals to, in turn, modulate downstream serotonergic/dopaminergic nuclei. The IPN predominantly houses GABAergic projection neurons (GPNs) and perturbation of their recruitment or activity precipitates emotion, reward and addiction phenotypes. Interestingly, the DDC possesses one of the highest densities of mu-opioid receptors (MORs) in the CNS. Although recently, conditional knockout mice have given important insight as to the behavioral role of MORs and MOR expressing neurons in the DDC, little is known regarding the function of this receptor at the granular circuit level. To fill this knowledge gap, we employed *in vitro* slice electrophysiology in adult mice combined with cell type specific optogenetics. Afferents to the IPN originate from two mHb populations; cholinergic (ChAT) and substance P (TAC1) neurons. Both types express VGluT1 and under our standard experimental conditions, light evoked EPSCs in GPNs are exclusively mediated by glutamate. MOR activation (DAMGO) elicits opposing effects characterized by inhibition and robust potentiation of AMPA receptor EPSCs mediated by TAC1 and ChAT neurons, respectively. As with glutamatergic transmission mediated by ChAT neurons, MOR activation also augments light-evoked nicotinic receptor EPSCs (experimentally uncovered by low concentration 4-AP in presence of glutamate receptor antagonists) on GPNs. In many brain regions, activation of mORs typically results in direct inhibition of excitability and neurotransmission in varied neuron subtypes. We have employed a combined pharmacogenetic approach utilizing alternate agonists (e.g. Met-ENK, morphine), antagonists (e.g. CTAP) and OPRM1 KO mice to establish this “non-canonical” effect of mORs in the DDC as a ground truth. Together, our observations identify a novel, unexpected role for MORs in boosting mHb ChAT neuronal recruitment of GPNs. Ongoing studies aim to determine (i) the locus of the mOR-mediated potentiation (e.g. pre- versus post-synaptic); (ii) whether the potentiation occurs during postnatal development to ascertain it's relevance in juveniles and (iii) determine if chronic nicotine or opioid administration hijacks/alters the mOR potentiation of cholinergic synaptic transmission. This intriguing interplay between the opioid and cholinergic systems likely warrants a re-evaluation of theoretical postulations regarding the neural correlates underlying the behavioral effects of mOR signaling in this critical addiction brain axes.

Disclosures: R. Chittajallu: None. **A. Vlachos:** None. **X. Yuan:** None. **S. Hunt:** None. **E. London:** None. **K.A. Pelkey:** None. **C.J. McBain:** None.

Poster

PSTR440: Modulation of Neurotransmission

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.06/B77

Topic: B.04. Synaptic Transmission

Support: German Research Foundation (DFG) grant SFB1286/B02

Title: Trafficking dynamics of synaptic adhesion proteins: neurexins and neuroligins frequently endocytose and recycle.

Authors: *C. BOGACIU, S. RIZZOLI;
Dept. of Neuro and Sensory Physiol., Univ. Med. Ctr. Göttingen, Göttingen, Germany

Abstract: Neurexins and neuroligins are pre- or post-synaptically expressed adhesion molecules, synthesized as heparan sulfate proteoglycans. They have a key role in the specification of synapse identity and connectivity, by the stabilization of axo-dendritic contacts. Adhesion molecules are known to use different routes of membrane trafficking, but these processes have not been studied extensively for neurexins and neuroligins. To address this, we tested their dynamics by relying on constructs carrying a small epitope tag (ALFA-tag). The tag was revealed with high specificity by a nanobody, which was imaged under both live-cell and fixed conditions, based on confocal and super-resolution microscopy. In a simple cell system (pheochromocytoma PC12 cells), we found that both sets of molecules were readily endocytosed, over a few hours, and that they recycled to the plasma membrane within 24 hours. The same observations were made in rat primary hippocampal neurons, albeit the recycling time frame was longer (up to 72 hours). Furthermore, we compared the neurexin and neuroligin dynamics at specific synapses with the local synaptic activity levels, using a synaptotagmin-based approach. We could observe a positive correlation between the neuroligin renewal at synapses and synaptic activity, suggesting that bigger and more active synapses will exhibit stronger neuroligin dynamics. The frequent endocytosis and re-surfacing of these molecules may serve their re-glycosylation, thereby constituting a way of saving energy, by renewing the glycan moieties of these proteins without the renewed synthesis of their peptide chains. These findings enlarge the field of synaptic recycling pathways and suggest the hypothesis that other synaptic surface molecules may follow a similar pathway.

Disclosures: C. Bogaciu: None. **S. Rizzoli:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

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Program #/Poster #: PSTR440.07/B78

Topic: B.04. Synaptic Transmission

Support: NICHD Z01-HD001205-27 Intramural Research Award
Center for Compulsive Behaviors Intramural Fellowship

Title: Divergent opioid-mediated suppression of inhibition between hippocampus and neocortex across species and development

Authors: *A. CACCAVANO[1], A. VLACHOS[1], J. KIM[1], V. MAHADEVAN[1], G. A. VARGISH[1], A. M. ROSSI[2], I. SPINEUX[2], J. WU[2], M. DAI[2], X. YUAN[1], S. P. HUNT[1], E. LONDON[1], R. CHITTAJALLU[1], K. A. PELKEY[1], G. J. FISHELL[2], C. J. MCBAIN[1];
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Abstract: Opioid receptors within the CNS regulate pain sensation and mood and are key targets for drugs of abuse. Within the adult rodent hippocampus (HPC), μ-opioid receptor agonists suppress inhibitory parvalbumin-expressing interneurons (PV-INs), thus disinhibiting the circuit. However, it is uncertain if this disinhibitory motif is conserved in other cortical regions, species, or across development. We observed that PV-IN mediated inhibition is robustly suppressed by opioids in HPC but not neocortex in mice and nonhuman primates, with spontaneous inhibitory tone in resected human tissue also following a consistent dichotomy. This hippocampal disinhibitory motif was established in early development when immature PV-INs and opioids were found to regulate primordial network rhythmogenesis. In adulthood, acute opioid-mediated modulation was partially occluded with morphine pretreatment, with implications for the effects of opioids on hippocampal network activity important for learning and memory. Ongoing experiments seek to determine the effects of chronic opioid exposure on the developing hippocampus. Together, these findings demonstrate that PV-INs exhibit a divergence in opioid sensitivity across brain regions that is remarkably conserved across evolution and highlights the underappreciated role of opioids acting through immature PV-INs in shaping hippocampal development.

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Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.08/B79

Topic: B.04. Synaptic Transmission

Title: Investigating synaptic interactions between neurons and small cell lung cancer

Authors: *A. HOUCEK[1], B. UZAY[2], L. M. MONTEGGIA[3], A. LINKOUS[4], E. T. KAVALALI[5];

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Abstract: Lung cancer is the leading cause of cancer-related deaths and has an extraordinary propensity to metastasize to the brain. While brain metastasis can produce several neurological symptoms including seizures, cancer cell affinity for cerebral tissue and subsequent integration with neurons remains poorly understood. Here, we address this question using small cell lung cancer (SCLC). Electrophysiological analysis of SCLC cells in neuronal microenvironments reveal functional synapse formation between neurons and adjacent SCLC cells. This synaptic integration of SCLC into neuronal microenvironments induces synaptic phenotypes and altered neuronal excitability in human induced neurons. Thus, in addition to established notions that neurological symptoms of brain metastasis are due to inflammation, compression, and edema, they may instead be explained in part by functional integration of cancer cells into neuronal networks. This finding reveals possible strategies to normalize aberrant tumor-induced augmentation of neuronal excitability.

Disclosures: A. Houcek: None. **B. Uzay:** None. **L.M. Monteggia:** None. **A. Linkous:** None. **E.T. Kavalali:** None.

Poster

PSTR440: Modulation of Neurotransmission

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.09/Web Only

Topic: B.04. Synaptic Transmission

Support: Beckman Scholar Award

Title: The effects of doxapram and its potential interactions with K2P channels in experimental model preparations

Authors: *K. BROCK[1], E. ELLIOTT[2], R. VASCASSENNO[4], R. L. COOPER[3], D. HARRISON[2];
[1]Biol., [3]Dept Biol, [2]Univ. of Kentucky, Lexington, KY; [4]Biol., Eastern Kentucky Univ., Versailles, KY

Abstract: The channels commonly responsible for maintaining cell resting membrane potentials are referred to as K2P (two-P-domain K+ subunit) channels. These K+ ion channels generally remain open but can be modulated by their local environment. These channels are classified based on pharmacology, pH sensitivity, mechanical stretch, and ionic permeability. Little is known about the physiological nature of these K2P channels in invertebrates. Acidic conditions depolarize neurons and muscle fibers, which may be caused by K2P channels given that one subtype can be blocked by acidic conditions. Doxapram is used clinically as a respiratory aid known to block acid-sensitive K2P channels; thus, the effects of doxapram on the muscle fibers

and synaptic transmission in larval Drosophila and crawfish were monitored. A dose-dependent response was observed via depolarization of the larval Drosophila muscle and an increase in evoked synaptic transmission, but doxapram blocked the production of action potentials in the crawfish motor neuron and had a minor effect on the resting membrane potential of the crawfish muscle. This indicates that the nerve and muscle tissues in larval Drosophila and crawfish likely express different K2P channel subtypes. Since these organisms serve as physiological models for neurobiology and physiology, it would be of interest to further investigate what types of K2P channels are expressed in these tissues.

Disclosures: K. Brock: None. **E. Elliott:** None. **R. Vascassenno:** None. **R.L. Cooper:** None. **D. Harrison:** None.

Poster

PSTR440: Modulation of Neurotransmission

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Program #/Poster #: PSTR440.10/B80

Topic: B.04. Synaptic Transmission

Support: Swedish research council. Dnr: 2020-00559

Title: Neurophysiological signatures in the basolateral amygdala associated with an AUD-like phenotype in rat

Authors: *D. CADEDDU, A. DOMI, E. LUCENTE, L. ADERMARK;
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Alcohol abuse is a major preventable factor for premature death and morbidity worldwide. The medical condition, characterized by the loss of control over alcohol use, is known as Alcohol Use Disorder (AUD) and can be diagnosed using the Diagnostic and Statistical Manual of mental disorders (DSM-5). While alcohol use in the population is common, only a subset of individuals develops AUD. To further outline neurobiological underpinnings associated with AUD, we used an AUD-based animal model to characterize interindividual variability to develop alcohol-addicted like behavior in rats, and combined behavioral tests with neurophysiological recordings performed in the basolateral amygdala (BLA), a brain region linked to reward seeking behavior and addiction. Rats were trained to self-administer alcohol in operant boxes for over two months and were then assessed focusing on three AUD-like behaviors based on the DSM-5. Specifically, we measured: i) persistence in alcohol-seeking when alcohol was not available, ii) motivation to self-administer alcohol under a progressive ratio schedule of reinforcement, and iii) maintenance of alcohol-seeking and taking despite punishment by electric foot-shock. The score assigned to each measure was then normalized (z-score) and the sum was used to calculate the global addiction score for each rat. Animals categorized into resilient, or vulnerable, to develop AUD-like behaviors were then selected together with water drinking control for in depth neurophysiological assessments using slice

electrophysiology. Whole cell patch clamp recordings were conducted in the BLA immediately after a session of alcohol self-administration. Electrophysiological recordings demonstrated that BLA neurons from animals displaying an AUD-vulnerable phenotype were characterized by a lower frequency of excitatory events compared to resilient rats. These neurons further demonstrated suppressed intrinsic excitability and fired fewer action potentials compared to both resilient and water drinking control rats. In conclusion, our data demonstrates that animals that exhibit an AUD-vulnerable phenotype also display an altered neurophysiological profile in the BLA, which in turn may play a key role in driving addictive behaviors.

Disclosures: D. Cadeddu: None. **A. Domi:** None. **E. Lucente:** None. **L. Adermark:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.11/B81

Topic: B.04. Synaptic Transmission

Support: NIH grant NS112292
NIH grant DA044121

Title: μ-opioid receptor modulation of the glutamatergic/gabaergic midbrain inputs to the mouse dorsal hippocampus

Authors: H. R. KIM[1], S. DEY[1], G. SEKERKOVA[1], *M. MARTINA[2];
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Abstract: While the general mechanisms of fast transmitter release are maintained in different synapses, glutamatergic and GABAergic synapses also show some important differences. In few cases, however, an individual synapse co-releases an excitatory (glutamate) and an inhibitory (GABA) neurotransmitter. The detailed mechanisms of this transmission are still incompletely described. We studied the mechanisms mediating neurotransmitter release and μ-opioid modulation at the dual glutamatergic/GABAergic inputs from the VTA and supramammillary nucleus to the dentate gyrus granule cells of dorsal hippocampus of male and female mice. In keeping with previous electron microscopy studies showing that in these synapses the two transmitters are released by separate active zones within the same terminals, we found that the short-term plasticity and pharmacological modulation of the glutamatergic and GABAergic currents are indistinguishable. We further found that glutamate and GABA release at these synapses are both virtually completely mediated by N- and P/Q-type calcium channels. We further found that activation of μ-opioid receptors strongly inhibits release by acting mostly on presynaptic N-type channels. However, the modulation by μ-opioid receptors is complex, as it appears to also include disinhibition due to down-modulation of local GABAergic interneurons which make direct axo-axonic contacts with the dual glutamatergic/GABAergic terminals.

Disclosures: H.R. Kim: None. **S. Dey:** None. **G. Sekerkova:** None. **M. Martina:** None.

Poster

PSTR440: Modulation of Neurotransmission

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Program #/Poster #: PSTR440.12/B82

Topic: B.04. Synaptic Transmission

Support: FAU Stiles-Nicholson Brain Institute

Title: Biphasic Activity in Co-Transmission of Glutamate and GABA

Authors: *B. KRUBITSKI[1], R. D. PENA[2];
[1]Florida Atlantic Univ. Neurosci. Grad. Program, Boynton Beach, FL; [2]Dept. of Biol. Sci., Florida Atlantic Univ., Jupiter, FL

Abstract: Co-transmission, the release of multiple neurotransmitters from a single neuron, is an increasingly recognized phenomenon in the nervous system. A particularly interesting combination of neurotransmitters exhibiting co-transmission are glutamate and GABA, which, when co-released from neurons, demonstrate complex biphasic activity patterns that varies depending on the time or amplitude differences from the excitatory (AMPA) or inhibitory (GABAA) signals. These differences can be interpreted through the lens of the postsynaptic neuron as complex temporal dynamics, adding or deleting specific spiking patterns. However, experimentally distinguishing whether this biphasic activity arises from co-transmission or from feed-forward inhibition or even from synaptic plasticity remains a significant challenge due to these patterns being degenerate. In this study, we employ a computational approach to distinguish these patterns based on specific dendritic filtering and the actual temporal integration of co-transmitted glutamate and GABA signals. We specifically focus on modeling the temporal filtering dynamics that arise from the many combinations of temporal and amplitude co-transmission differences. We also identify a number of summation patterns resembling high-pass, band-pass, and low-pass filters, which have been previously attributed to the interplay between short-term synaptic plasticity mechanisms and the intrinsic active and passive electrical properties of the postsynaptic dendritic membrane. By examining these filtering effects in the context of temporal summation, we determined the extent to which a postsynaptic signal can be ascribed to short-term plasticity, co-transmission, or feed-forward inhibition. To achieve this, our methods also included the implementation of an extended Markram-Tsodyks short-term plasticity model that captures similar dynamics of multiple co-transmitted neurotransmitters and their interactions. Our computational framework provides insights into the complex interplay between co-transmission, short-term plasticity, and dendritic filtering, offering a mechanistic understanding underlying the integration and processing of co-transmitted signals in neural circuits.
Acknowledgments: This work was supported by the FAU Stiles-Nicholson Brain Institute.

Disclosures: B. Krubitski: None. **R.D. Pena:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.13/B83

Topic: B.04. Synaptic Transmission

Support: NIH R01DK130246

Title: Sex differences in diet-induced alterations in the function of nucleus accumbens medium spiny neurons

Authors: *M. ORTEGO-DOMINGUEZ, L. M. RAYCRAFT, C. R. FERRARIO;
Dept. of Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: Obesity is one of the most prevalent diseases worldwide, and increases the risk of type II diabetes, dyslipidemia, hypertension, and some cancers in people. In rodents that are prone to diet-induced obesity (obesity-prone), consumption of obesogenic foods (i.e., high-fat, high-sucrose diets) alters the function of the nucleus accumbens (NAc) in ways that are expected to further promote over-eating. For example, brief consumption of a 'junk-food' (JF) diet increases protein expression and synaptic transmission mediated by calcium-permeable AMPA receptors (CP-AMPAR) in the NAc core of obesity-prone males and females. This increase in CP-AMPAR synaptic transmission requires a brief removal of the JF diet (24-48 hours ad libitum standard chow), and persistd for several weeks in males, but not females. NAc CP-AMPARs are required for the expression of cue-triggered food-seeking in males, suggesting that JF induced enhancements in this receptor population may promote food-seeking in response to food-cues. In addition, this same diet manipulation also reduces intrinsic excitability of NAc medium spiny neurons (MSNs) in both sexes. However, it is unclear whether this reduction in intrinsic excitability is sufficient to compensate for the presumed increase in excitatory drive due to increases in CP-AMPAR transmission. Therefore, here we used whole-cell patch clamping approaches to determine the net effect of JF diet consumption on the ability of excitatory glutamate inputs to drive activity of NAc MSNs. Briefly, adult male and female obesity-prone rats were given free access to JF for 10 days while controls were maintained on standard lab chow. Next, rats in the JF groups were given a brief (24-48 hours) JF deprivation period in which they only had access to standard lab chow. Finally, coronal sections containing the NAc core were prepared, and recordings were made from MSNs to assess changes in membrane potential in response to varying electrical stimulation (input/output) or current injection (I/V), as well as passive cell properties, and excitatory/inhibitory balance. Preliminary data from chow fed controls suggest that in males, the input/output curve is shifted to the left, compared to the females, such that lower intensity stimulation produces larger changes in membrane depolarization. It's predicted that this sex difference will persist following JF diet consumption, but that responsivity of MSNs to stimulation of excitatory inputs will be enhanced in JF vs chow

groups. Data will be discussed in light of established sex differences in NAc function, and sex differences in motivation for food.

Disclosures: M. Ortego-Dominguez: None. **L.M. Raycraft:** None. **C.R. Ferrario:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.14/B84

Topic: B.04. Synaptic Transmission

Support: Chungbuk National University Korea National University Development Project 2021

Title: Optogenetic inhibition of glutamatergic neurons in the dysgranular posterior insular cortex alleviates trigeminal neuropathic pain

Authors: *M. RAHMAN[1], J. ISLAM[2], E. KC[3], Y. PARK[4];
[1]Chungbuk Natl. Univ., 1 Chungdaero, Gaesin-dong, Cheongju-si,, Korea, Republic of; [2]Dept. of Neurosci., Col. of Med., Chungbuk Natl. Univ., Cheongju, Korea, Republic of; [3]Med. (Program in Neuroscience), Chungbuk Natl. Univ., Cheongju, Korea, Republic of; [4]Neurosurg., Chungbuk Natl. Univ. Hosp., Neurosurg., Cheongju-Si, Korea, Republic of

Abstract: In individuals with chronic neuropathic pain, the posterior insular cortex (PIC) has been found to exhibit increased glutamatergic activity, and the dysgranular portion of the PIC (DPIC) has been investigated as a novel putative cortical target for pain modulation. However, the role of DPIC glutamatergic neurons (DPICg) in trigeminal neuropathic pain (TNP) modulation remains unclear. In this study, we examined the outcomes of DPICg inhibition in a rat model of chronic constriction injury of the infraorbital nerve (CCI-ION). Animals were randomly divided into TNP, sham, and naïve groups. TNP animals underwent CCI-ION surgery; the sham and naïve groups served as controls. Either optogenetic or null viral vectors were delivered to the contralateral DPICg of TNP and sham animals. In vivo single-unit extracellular recordings from the ipsilateral spinal trigeminal nucleus caudalis (TNC) and contralateral ventral posteromedial (VPM) thalamus were obtained under both "ON" and "OFF" stimulation states. Behavioral responses during the stimulation-OFF and stimulation-ON phases were examined. Expression of c-Fos, pERK, and CREB immunopositive neurons was also observed. Optogenetic inhibition of contralateral DPICg decreased the neural firing rate in both the TNC and VPM thalamus, the expression of sensory-responsive cell bodies, and transcriptional factors in the DPIC of the TNP group. Improvements in hyperalgesia, allodynia, and anxiety-like responses in TNP animals were also observed during the stimulation-ON condition indicating an antinociceptive effect. In fine, descending pain processing signaling is influenced by neuroanatomical projections from the DPIC to the pain matrix areas, and DPICg could play a

necessary role in this neural circuitry. Therefore, the antinociceptive effect of DPICg inhibition in this study may provide evidence for the therapeutic potential of DPICg in TNP.

Disclosures: M. Rahman: None. **J. Islam:** None. **E. Kc:** None. **Y. Park:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.15/B85

Topic: B.04. Synaptic Transmission

Support: European Research Council (ERC): No 692692, AdG "GIANTSYN"
Austrian Science Fund (FWF): Z 312-B27, Wittgenstein Award
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Austrian Science Fund (FWF): PAT 4178023

Title: Presynaptic mechanisms underlying $GABA_B$ receptor-mediated heterosynaptic depression at hippocampal mossy fiber bouton to CA3 pyramidal neuron synapses

Authors: *P. LIN[1], K. LICHTER[1], Y. OKAMOTO[1,2], P. JONAS[1];
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Abstract: The hippocampal mossy fiber bouton to CA3 pyramidal neuron (MFB-CA3 PN) synapse plays an important role in hippocampal information processing. The efficacy of this key synapse is under profound modulation. Activation of presynaptic $GABA_B$ receptors ($GABA_B$Rs) reduces extracellularly evoked EPSC amplitudes and mediates heterosynaptic depression at MFB-CA3 PN synapses (Vogt and Nicoll, 1999, PNAS 96, 1118-1122; Guetg et al., 2009, J. Neurosci. 29, 1414-1423). To dissect the mechanisms underlying $GABA_B$R-mediated modulation at these synapses, we performed paired pre-postsynaptic patch-clamp recordings and ultrastructural analysis using cryo-fixation and 2D electron microscopy (EM) in acute slices of mouse hippocampus. 50 µM of the $GABA_B$R agonist baclofen suppressed the evoked EPSC amplitudes by 88.3 ± 2.2% (n = 9 pairs, $p < 0.01$). Coefficient-of-variation analysis indicated that baclofen had a presynaptic site of action. The presynaptic Ca^{2+} currents evoked by action potential waveforms were reduced by 32.2 ± 3.0% (n = 3, $p < 0.05$), only partially accounting for the reduction in EPSC amplitudes. Cumulative EPSC analysis using train stimulation revealed that presynaptic $GABA_B$R activation significantly reduced the size of readily releasable pool (RRP) by 72.1 ± 6.9% (n = 9, $p < 0.01$). Moreover, the RRP refilling rate was reduced by 33.0 ± 6.8% (n = 9, $p < 0.01$), while the vesicular release probability decreased by 54.6 ± 4.4% (n = 9, $p < 0.01$). EM analysis of baclofen-incubated (50 µM, 5 min) and cryo-fixated acute hippocampal slices revealed a median of 0.27 docked vesicles (0-5 nm) per 100 nm active zone profile length compared to 0.51 docked vesicles under control conditions ($p < 0.01$), suggesting that baclofen may decrease the docked vesicle pool in MFB active zones. Pre-postsynaptic recordings

combined with optogenetic stimulation of hippocampal GABAergic interneurons suggested that synaptically released GABA inhibited evoked EPSC amplitudes at MFB-CA3 PN synapses by ~50%, implying a physiological role of $GABA_BR$-mediated regulation. Collectively, our results suggest that presynaptic $GABA_BRs$, activated by endogenous GABA, shape synaptic efficacy via regulation of vesicular release mechanisms at hippocampal MFB-CA3 PN synapses.

Disclosures: P. Lin: None. **K. Lichter:** None. **Y. Okamoto:** None. **P. Jonas:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.16/B86

Topic: B.04. Synaptic Transmission

Support: NIH Grant R01 MH124934

Title: Pharmacology of cholinergic and serotonergic modulation of commissural excitatory afferents to the mouse prefrontal cortex

Authors: *E. LIU, A. T. GULLEDGE;
Geisel Sch. of Med. at Dartmouth Col., Hanover, NH

Abstract: Cortical release of acetylcholine (ACh) and serotonin (5-HT) contribute to a variety of cognitive processes. In the mouse prefrontal cortex (PFC), these transmitters exhibit well described cell-type-specific regulation of postsynaptic neuronal excitability. However, receptors for both ACh and 5-HT are also expressed presynaptically at many cortical synapses, and both transmitters can suppress action-potential-dependent glutamate release at corticocortical excitatory synapses. To determine the receptor subtypes that mediate cholinergic and serotonergic modulation of synaptic transmission, we recorded light-evoked excitatory postsynaptic potentials (EPSPs) generated by two 1-ms flashes of blue light (20 Hz) in layer 5 pyramidal neurons in the *ex vivo* PFC from adult female and male mice previously injected unilaterally in the PFC with an AAV expressing channelrhodopsin-2. Under control conditions, 1 µM ACh (with 10 µM eserine) strongly suppressed light-evoked EPSPs in layer 5 pyramidal neurons by 73 ± 12% (mean ± SD), from a mean of 8.3 ± 3.2 mV to 2.1 ± 1.2 mV (n = 15). The paired-pulse ratio (PPR) also increased from 1.54 ± 0.24 to 2.10 ± 0.54. In the presence of AF-DX 116 (5 µM), an antagonist somewhat selective for the M2-type muscarinic ACh receptor (mAChR), 1 µM ACH moderately reduced the first EPSP amplitude by 31 ± 7%, from 8.9 ± 2.7 to 6.1 ± 1.6 mV and increased the PPR from 1.72 ± 0.18 to 1.95 ± 0.29 (n = 8). On the other hand, the presence of VU6028418 (5 µM), an antagonist preferential to M4-type mAChRs, the effect of 1 µM ACh was largely curtailed, with EPSPs in the presence of ACh (6.3 ± 1.8 mV) being similar to those measured with the antagonist alone (6.9 ± 2.2 mV; mean reduction of 8 ± 10%) and PPR decreasing from 1.82 ± 0.27 in baseline conditions to 1.73 ± 0.25 in the presence of ACh (n = 8). Further, the M4 positive allosteric modulator (VU0467154, 3 µM) potentiated

the impact of 1 µM ACh, with EPSPs being reduced by 86 ± 8%, from 7.1 ± 2.0 to 1.0 ± 0.8 mV, and PPR becoming much more variable after ACh application (from 1.35 ± 0.34 to 1.60 ± 0.79; n = 8). Light-evoked COM EPSPs were also suppressed by 5-HT. At a concentration of 2 µM, 5-HT suppressed EPSPs by 68 ± 15%, from 8.2 ± 3.9 to 2.5 ± 1.7 mV and increased PPR from 1.50 ± 0.22 to 1.76 ± 0.51 (n = 21). The effect of 5-HT was antagonized by 10 µM SB216691 (SB; n = 10), a 5-HT_{1B} receptor blocker, with EPSPs being reduced only by 15 ± 13% (from 10.5 ± 3.8 mV in baseline conditions to 8.7 ± 3.0 mV in the presence of SB), and PPR being similar (1.44 ± 0.20 and 1.49 ± 0.26) in both conditions. These data suggest that glutamate release from COM afferents in the mouse PFC is regulated by ACh and 5-HT via presynaptic expression of M4 and 5-HT_{1B} receptors, respectively.

Disclosures: E. Liu: None. **A.T. Gulledge:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.17/B87

Topic: B.04. Synaptic Transmission

Title: Enduring impact of psilocybin on synaptic physiology across medial prefrontal cortical layers

Authors: *A. S. TIEMROTH[1,2], Y.-Y. HSIAO[3], E. VASQUEZ[3], M. DE SOUZA FONSECA[3], A. M. GOMEZ[1,3];
[1]Helen Wills Neurosci. Inst., [2]Neurosci., [3]Mol. and Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: Synaptic plasticity enables neural circuits to adjust synaptic weights between cells, refining circuit communication in response to changing inputs. Psychedelics robustly engage the serotonergic system and are potent neuromodulators that increase plasticity in humans and mice. While these compounds rapidly modulate cellular excitability upon receptor binding, emerging evidence indicates that psychedelics induce lasting changes to synaptic gene expression and plasticity that persist in the prefrontal cortex for days to weeks following a single exposure. Although these findings suggest changes to prefrontal cortex function, the impact on synaptic physiology remains unclear. The goal of our study is to determine the enduring impact of a single psychedelic dose on synaptic transmission in the input and output layers of the medial prefrontal cortex (mPFC). Here, we used slice electrophysiology in transgenic mouse lines to measure intrinsic and synaptic properties of mPFC cell types in layer 2/3 and layer 5 at key time points following exposure to the serotonergic psychedelic psilocybin. We performed treatment blinded whole-cell patch-clamp recordings in transgenically labeled mPFC cell types in both male and female adult mice at 2 hours, 48 hours, and 1 week after intraperitoneal injection of psilocybin (2mg/kg) or saline. We find that psilocybin alters synaptic activity of layer 2/3 parvalbumin interneurons at acute (2 hours) and prolonged (48 hours) time points, but modulates

intrinsic properties exclusively at 48 hours. Importantly, we find that psilocybin differentially affects excitatory and inhibitory synaptic activity onto parvalbumin interneurons. These results indicate that psilocybin exerts cell type-specific effects on synaptic transmission that occur days after exposure. Work is ongoing to compare these effects across cortical layers. In sum, we reveal that a single psychedelic dose is sufficient to alter long-term microcircuit activity in the mPFC.

Disclosures: A.S. Tiemroth: None. **A.M. Gomez:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.18/B88

Topic: B.04. Synaptic Transmission

Support: NIH Grant MH122461

Title: Serotonergic modulation of the excitability of claustrum neurons in male rats

Authors: *R. ROULEAU[1], S. OUBRAIM[2], R.-Y. SHEN[3], S. HAJ-DAHMANE[4];
[1]Univ. at Buffalo, Buffalo, NY; [2]Dept. of Pharmacol. and Toxicology, Univ. At Buffalo, Buffalo, NY; [3]Res. Inst. on Addictions, Univ. at Buffalo, Buffalo, NY; [4]Dept. of Pharmacol. and Toxicology, Univ. of Buffalo, Buffalo, NY

Abstract: The claustrum, a thin, condensed sheet of neurons highly interconnected with cortical areas, plays an essential role in gating higher cognitive functions such as sensation, perception, and attention. Previous studies have shown that the claustrum receives strong input from serotonin (5-HT) neurons of dorsal raphe nucleus (DRN) and highly expresses 5-HT2A receptors, the main target of psychedelics. However, the mechanisms by which 5-HT and serotonin psychedelics, regulates neuronal excitability and synaptic processing in the claustrum are unknown. Using ex-vivo whole cell recordings, we examined the impact of 5-HT on the intrinsic excitability and synaptic inputs of claustral neurons. Our results revealed four physiologically distinct groups of neurons: type I & II regular firing, adapting, and fast-spiking neurons. Bath application of 5-HT (30 µM) hyperpolarized and depolarized these neurons via 5-HT1ARs and 5-HT2ARs, respectively. We then examined the impact of 5-HT on excitatory synaptic transmission. We found that 5-HT (30 µM) depressed the amplitude of evoked excitatory synaptic currents (eEPSCs) and increased paired-pulse ratio. These effects were blocked and mimicked by 5-HT2AR antagonist and agonist MDL (3 µM) and TCB2 (3 µM) respectively, indicating that activation of 5-HT2ARs depresses glutamate release in the claustrum. Consistent with this notion, 5-HT (30 µM) and TCB2 (3 µM) significantly reduced the frequency, but not the amplitude of miniature excitatory synaptic currents via activation of 5-HT2ARs. Examination of the mechanisms by which 5-HT2ARs depresses glutamate release showed that this effect was not signaled post-synaptic G-protein activation nor by retrograde

endocannabinoid signaling. Taken together, our results unravel the cellular mechanisms by which 5-HT2Rs regulate the excitability of claustral neurons and gate their excitatory inputs.

Disclosures: R. Rouleau: None. **S. Oubraim:** None. **R. Shen:** None. **S. Haj-Dahmane:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.19/B89

Topic: B.04. Synaptic Transmission

Support: Neukom Institute Postdoctoral Fellowship
Neukom Institute CompX Grant
NIH 5P20GM113132
NIH R44 MH116748

Title: Optical physiology reveals bidirectional modulation of glutamate release by subthreshold electric field stimulation

Authors: *A. S. ABERRA, L. W. MILES, M. B. HOPPA;
Biol. Sci., Dartmouth Col., Hanover, NH

Abstract: Subthreshold electric fields (E-fields) fail to directly stimulate neuronal firing but have been shown to powerfully modulate ongoing brain activity. While E-fields are known to polarize membranes, the mechanisms by which individual neurons respond to subthreshold E-fields remain unclear, especially at the subcellular level of axons. Previous experimental work showed somatic and dendritic polarization by subthreshold E-fields alters postsynaptic integration, but axonal polarization and its effects on presynaptic transmission have not been measured. This is primarily due to the inaccessibility of fine axon terminals to electrical recording techniques. Here, we used genetically encoded optical indicators of voltage, glutamate, and calcium to measure subcellular effects of spatially uniform electric fields in cultured hippocampal neurons. Voltage imaging revealed a biphasic polarization distribution across neuronal morphologies, with depolarization at the cathodal and hyperpolarization at the anodal end, in agreement with compartmental modeling predictions. By imaging glutamate release (iGluSnFR3) in individual presynaptic boutons, we found subthreshold E-fields (5, 25, and 50 V/m) exerted bidirectional facilitation or suppression of glutamate release, depending on polarity. Facilitation had a nonlinear dependence on intensity, with over 70% of synapses significantly facilitated at 25 and 50 V/m, while 5% were facilitated at the lowest intensity tested (5 V/m). While many theories of subthreshold modulation of synaptic transmission predict axonal polarization alters AP waveform shape and subsequently synaptic strength, we did not observe significant changes in AP width using voltage imaging in the axon. Additionally, depolarization due to high frequency activity is known to inactivate axonal Kv1 channels, causing AP broadening and synaptic facilitation; however, we found shRNA-mediated

knockdown of Kvbeta1 subunits had no effect on E-field-induced facilitation of glutamate release. Our results instead suggest that slight changes in calcium channel gating kinetics are the target of E-Fields that can exert bidirectional control of neurotransmitter release. In addition, this work establishes a platform for studying acute effects of electric fields on single neurons at the subcellular level.

Disclosures: A.S. Aberra: None. **L.W. Miles:** None. **M.B. Hoppa:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.20/B90

Topic: B.04. Synaptic Transmission

Title: Repeated fentanyl administration dysregulates excitatory and inhibitory transmission and causes glial cell activation in the hippocampus CA1 region in rats

Authors: *G. ROCHA-BOTELLO[1], V. A. MARTINEZ-ROJAS[2], S. L. CRUZ[3], E. J. GALVAN[4];
[1]Ctr. de Investigación y Estudios Avanzados, Ciudad de México, Mexico; [2]Cinvestav Sede Sur, Mexico City, Mexico; [3]Pharmacobiology, CINVESTAV, IPN, Mexico City, Mexico; [4]Farmacobiologia, CINVESTAV SUR, Mexico City, Mexico

Abstract: Fentanyl is both a valuable therapeutic agent and a misused drug. Its non-medical use has recently been responsible for an increase in opioid-related overdose deaths. Despite its medical and non-medical widespread use, there is little evidence regarding the effects of fentanyl on synaptic transmission in the central nervous system. This work investigates the impact of repeated fentanyl administration on the synaptic transmission in the area CA1 of the hippocampus. We treated Sprague-Dawley rats with fentanyl (0.1 mg/kg, ip) or saline solution for seven days until completing 19 administrations. Two hours after the last fentanyl injection, we obtained dorsal hippocampal slices to conduct whole-cell patch clamp and extracellular recordings or immunofluorescence assays to mark microglia (CD11B) and astrocytes (GFAP). Fentanyl reduced the amplitude of the inhibitory postsynaptic potential (fIPSP) and excitatory postsynaptic potential (fEPSP), as well as the somatic population spike (PS). These results indicate a decrease in GABAergic inhibition, the strength of synaptic transmission, and somatic output. Repeated fentanyl exposure also altered short and long-term synaptic plasticity since acute slices from fentanyl-treated animals showed increased paired-pulse ratio and a decreased induction of theta burst-mediated LTP compared to control slices. Consistent with these results, fentanyl treatment weakened passive membrane properties including resting membrane potential and somatic input resistance assessed with patch-clamp recordings. Likewise, we observed an increase in the rheobase current to elicit action potentials and a reduction in the firing frequency of the fentanyl-treated animals. On the other hand, fentanyl caused an increase in the microglia and astrocytes' immunoreactivity, suggesting an inflammatory process. In conclusion, our data

show that repeated fentanyl exposure alters the strength of synaptic transmission and output of pyramidal cells of the hippocampus and induces neuroinflammation.

Disclosures: G. Rocha-Botello: None. **V.A. Martinez-Rojas:** None. **S.L. Cruz:** None. **E.J. Galvan:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.21/B91

Topic: B.04. Synaptic Transmission

Support: NIH grant HL 146833

Title: Hypertension increases sympathetic neuron activity by enhancing intraganglionic cholinergic collateral connections

Authors: *M.-H. LI;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Hypertension increases sympathetic neuron activity by enhancing intraganglionic cholinergic collateral connections

Minghua Li[1], Michelle Sorensen[1], Morgan A. Johnson1, Susan L. Ingram[2], Michael C. Andresen[1], and Beth A. Habecker[1]
[1]Department of Chemical Physiology and Biochemistry, Oregon Health and Science University, Portland, OR, United States of America, 97239. [2]Department of Anesthesiology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045

AbstractAutonomic dysregulation, including sympathetic hyperactivity, is a common feature of hypertension (HT) and other cardiovascular diseases. The central nervous system (CNS) plays a role in driving chronic sympathetic activation in disease, but several lines of evidence suggest that neuroplasticity in the periphery may also contribute. The potential contribution of postganglionic sympathetic neurons to sustained sympathetic hyperactivity is not well understood. We recently discovered that noradrenergic sympathetic neurons in the stellate ganglion (SG) have excitatory cholinergic collateral connections to other neurons within the ganglion. We hypothesize that remodeling of these neurons and increased cholinergic collateral transmission contributes to sustained sympathetic hyperactivity in cardiovascular diseases including HT. To test that hypothesis, we examined activity of sympathetic neurons in isolated SG in control conditions and after one week of HT induced by peripheral angiotensin II (AngII) infusion, using whole-cell patch-clamp recordings. Despite the absence of central inputs, we observed elevated spontaneous activity and synaptic transmission in sympathetic SG neurons from hypertensive mice that required generation of action potentials. Genetically disrupting cholinergic transmission in noradrenergic neurons decreased basal neuronal activity and prevented AngII -mediated enhancement of activity. Similar changes in activity, driven by

increased collateral transmission, were identified in cardiac projecting neurons and neurons projecting to brown adipose tissue. These changes were not driven by altered A-type K^+ currents. This suggests that HT stimulates increased activity throughout the intraganglionic network of collateral connections, contributing to the sustained sympathetic hyperactivity characteristic in cardiovascular disease.

Disclosures: M. Li: None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.22/B92

Topic: B.04. Synaptic Transmission

Support: NIH Grant R25NS114309

Title: Studying the dysfunction of intellectual-disability linked mutations in the PP2A B' subunit, and how they affect synaptic transmission.

Authors: *B. I. ALDRIDGE[1], C. WU[2];
[1]Neurosci., LSU Hlth. Sci. Ctr. New Orleans, New Orleans, LA; [2]Neurosci. Ctr., LSU Hlth. Sci. Ctr., New Orleans, LA

Abstract: Bryson Aldridge[1]Xavier University of Louisiana[1], New Orleans, Louisiana, 70125
Chunlai Wu[2]LSU Health Neuroscience Center of Excellence[2]
Studying the dysfunction of intellectual-disability-linked mutations in the PP2A B' subunit - how they affect synaptictransmission
Studies in patients with intellectual disabilities have identified a series of 7 different missense and deletion mutations in human *PPP2R5C* and *PPP2R5D* genes. *PPP2R5C* and *PPP2R5D* are human genes that share a homolog with the *well-rounded* (*wrd*) gene in fruit flies. These genes encode the regulatory subunit of the PP2A enzyme, which is responsible for PP2A subcellular localization and substrate recognition. The Wu lab's studies on *wrd* demonstrated that the synaptic master organizer, Liprin-α, recruits Wrd to the synapses, where Wrd-PP2A mediates dephosphorylation events crucial for structural plasticity at the nerve terminals. Loss of *wrd* function reduces the size of the presynaptic terminal, destabilizes active zones at the larval glutamatergic neuromuscular junctions, diminishes light-induced remodeling of active zones at the photoreceptor synapses, and impairs gustatory learning in the adult. My research project will focus on studying the synaptic functional defects induced by these ID-linked mutations in *wrd* through electrophysiological recording of the larval NMJs. I will first establish the rescue of *wrd* null electrophysiological phenotypes at the larval NMJs by expressing wild type *UAS-Wrd* transgene in the muscle of *wrd* mutants. I will then perform the same rescuing experiments using *UAS-Wrd* transgenes each carrying a mutation mimicking those identified in the human

PPP2R5C/*PPP2R5D*-linked ID patients. This data will determine which of the 7 ID-linked mutations in *wrd* affect synaptic transmission at the larval NMJs.

Disclosures: B.I. Aldridge: None. **C. Wu:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.23/B93

Topic: B.04. Synaptic Transmission

Support: NIH intramural grant

Title: Synaptic RNA Dynamics Under Alcohol Exposure: Implications for Alcohol Use Disorder Pathophysiology

Authors: *Y. JOO, Y. JUNG, D. GOLDMAN;
NIH/NIAAA, Rockville, MD

Abstract: RNA localization within synaptic regions has been demonstrated through advanced techniques like transcriptomic analysis and super-resolution microscopy. Synaptic RNA may play crucial roles in the rapid and flexible functioning of neurons in response to activity. Dysfunctions in their localization within synaptic regions may be implicated in aberrant signaling transmission. Alcohol Use Disorder (AUD) manifests diverse clinical symptoms including increased neural damage, alcohol consumption, decreased cognitive function, and abnormal mood. Moreover, alcohol has been shown to modulate synaptic plasticity and function. Transcriptomic alterations have been observed in both human patients and animal models of AUD. However, the impact of alcohol on RNA localization and expression within synaptic regions remains unknown. In this study, we utilized various mouse brain tissues, including the hippocampus, cortex, and striatum, following chronic ethanol exposure. Synaptosomal fractionation was conducted, and transcriptomic analyses were performed on RNA extracted from both synaptosomal and homogeneous samples. While 15,777 genes were initially detected in the control group, synaptosomal enrichment yielded 15,557 genes, with an overlap of 15,105 genes and unique sets of 672 and 452 genes in the homogeneous and synaptosomal samples, respectively. By employing Synaptic Gene Ontologies and annotations (SynGO) on synaptosomal samples compared to controls, we identified the top 1,000 genes significantly enriched in synaptic functions, highlighting the synaptic compartment's importance in mRNA composition. We observed a substantial reduction in the number of unique RNA species in synaptosome-enriched samples following alcohol exposure, suggesting alcohol-induced alterations in synaptic mRNA composition. Among the genes showing differential significance between alcohol-treated and control groups in the hippocampus, a subset mapped to SYNGO-annotated genes involved in synaptic vesicle exocytosis regulation, such as SNAPIN and SYN3, along with genes related to translation regulation. These findings suggest that alcohol may

disrupt synaptic mRNA composition, potentially impacting synaptic transmission and local translation, contributing to the pathogenesis of Alcohol Use Disorder.

Disclosures: Y. Joo: None. **Y. Jung:** None. **D. Goldman:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.24/B94

Topic: B.04. Synaptic Transmission

Support: NIH-MH R01MH119355
NIH-NINDS R01NS097312
NIH-NIDA R01DA048822
W911NF2110328

Title: Distinct endocannabinoids specifically signal to astrocytes and neurons

Authors: *J. A. NORIEGA-PRIETO[1,2], R. FALCON-MOYA[1,2], P. KOFUJI[1,2], A. ARAQUE[1,2];
[1]Neurosci., [2]Univ. of Minnesota, Minneapolis, MN

Abstract: The endocannabinoid (eCB) system is an essential intercellular signaling mechanism with a decisive role in many physiological functions of the brain. Neuron-released eCBs can depress synaptic transmission by directly activating presynaptic neuronal CB1 receptors (CB1Rs), and they can indirectly potentiate adjacent synapses by activating astrocytic CB1Rs. In contrast to most, if not all, neurotransmitter systems, the eCB system in the brain involves two distinct endogenous ligands, 2-arachidonoylglycerol (2AG) and anandamide (AEA), and a main receptor (CB1R). The physiological meaning of this particularity remains unknown. Here we show that the different eCBs selectively signal to either astrocytes or neurons, inducing distinct and contrasting synaptic regulation. Combining two-photon imaging, pharmacological and optogenetic approaches, and transgenic mice for the synthesis enzyme of both eCBs, we show that preventing 2AG synthesis abolished the synaptic depression, which was mediated exclusively by neuronal mechanisms. In contrast, preventing the AEA synthesis abolished the lateral synaptic¬¬¬ potentiation, which was mediated by astrocyte calcium mobilization. Finally, we show that the synthesis of AEA, but not 2AG, and the astrocyte-mediated signaling are required for the hippocampal long-term potentiation induced by a spike-timing-dependent plasticity protocol. Hence, while 2AG selectively signals to neurons, AEA specifically signals to astrocytes, thus evoking contrasting regulatory phenomena of synaptic transmission and plasticity. These results demonstrate the existence of separate cellular signaling pathways that differently involve distinct eCBs, which selectively act on either neurons or astrocytes.

Disclosures: J.A. Noriega-Prieto: None. **R. Falcon-Moya:** None. **P. Kofuji:** None. **A. Araque:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.25/B95

Topic: B.04. Synaptic Transmission

Support: NIH NIA T32 fellowship T32 AG000266

Title: The role of N6-methyladenosine (m^6A) mRNA modification in the regulation of synaptic activity

Authors: *O. A. MALAK[1], G. KAUWE[2], E. C. LAI[3], P. HAGHIGHI[1];
[1]Buck Inst. for Res. on Aging, Novato, CA; [2]Buck Inst., Novato, CA, ; [3]Developmental Biol., Mem. Sloan Kettering Cancer Ctr., New York, NY

Abstract: Olfat A. Malak[1], Lijuan Kan[2], Eric C. Lai[2], Pejmun Haghighi[1].
Neurotransmitter release at synaptic terminals is a meticulously regulated mechanism that allows neurons to communicate with one another and with their target tissues. Disruption in this regulation has detrimental consequences on neural communication and circuit function and is associated with developmental and neurodegenerative diseases. Although many proteins are known to be involved in the control of neurotransmitter release, the molecular programs that orchestrate their expression are not well defined. Here, we hypothesize that N6-methyladenosine (m^6A) modification of mRNA is one such molecular program. We combine electrophysiology and biochemistry with powerful genetic tools in the *Drosophila* system, in vivo, to reveal how m^6A modification regulates synaptic activity at the *Drosophila* larval neuromuscular junction (NMJ). Our results 1) show that mutations of m^6A factors alter normal synaptic function at NMJ and 2) define a new regulatory mechanism by which m^6A influences neurotransmitter release. Our work provides a conceptual advance in our understanding of the regulation of neuronal activity and points to dysregulation in m^6A modification as a potential contributor to age-dependent nervous system diseases.

Disclosures: O.A. Malak: None. **G. Kauwe:** None. **E.C. Lai:** None. **P. Haghighi:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.26/B96

Topic: B.04. Synaptic Transmission

Support: CAPES (#88887.635569/2021-00)
FAPESP (#2018/15957-2)
CNPq (#309338/2020-4)

Title: Electrophysiological evaluation of neuron-astrocyte interaction in the Nucleus Tractus Solitarius of mice exposed to sustained hypoxia

Authors: *M. S. LUZ[1], D. ACCORSI-MENDONCA[2], B. H. MACHADO[3];
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Abstract: The Nucleus Tractus Solitarius (NTS) is critical for cardiorespiratory regulation and astrocytes play an important modulatory role in the synaptic transmission in this nucleus. Glutamate is the main excitatory neurotransmitter and extracellular levels are regulated by astrocytic glutamate transporters (GLT-1 and GLAST). Our aims were: a) to characterize neuron-astrocyte interaction in the NTS of control mice and b) to evaluate the effect of sustained hypoxia (SH) on glutamatergic transmission in the NTS of mice and its modulation by astrocytes. NTS brainstem slices were obtained from mice after normoxia (control; FiO_2=0.21-24h) or SH (FiO_2=0.10-24h). Electrophysiological properties of neurons and astrocytes were evaluated using whole-cell patch-clamp. All protocols were approved by the institutional ethics committee (#073/2021). In control mice the majority of astrocyte glutamate transporter activity is mediated by GLT-1 [D-aspartate: -57.19±17.8 pA (n=5) vs D-aspartate + Dihydrokainic acid (DHK-300 µM) -19.05±9.5 pA (n=5)]. The neuron-astrocyte interaction is present in control mice since the inhibition of GLT-1 affected the neuronal properties, such as resting membrane potential [aCSF: -82.75±4 mV (n=15) vs DHK: -70.95±5 mV (n=15)] and amplitude of glutamatergic currents in neurons evoked by Tractus Solitarius (TS) stimulation [aCSF: -87.66±23.3 pA (n=12) vs aCSF + DHK: -139.3±45.9 pA (n=12)]. SH increased the amplitude of TS-evoked glutamatergic current [control: -53.2±15 pA (n=17) vs SH: -84±15 pA (n=18)]. We evaluated if this increase was related to changes in astrocyte glutamate transporter activity or in the pre-synaptic release of glutamate. The neuron-astrocyte interaction after SH was not altered because no changes were observed in the astrocyte glutamate transporter activity [control: -38±6 pA (n=31) vs SH: -49±9 pA (n=15)]. SH also produced no changes in the pre-synaptic neuronal parameters related to: 1) the glutamate release [$1/CV^2$ - control: 37.2±10 (n=12) vs SH: 56.4±18 (n=14)]; 2) paired pulse ratio - control: 0.78±0.09 (n=15) vs SH: 0.62±0.04 (n=15) and 3) short-term depression - control: 59±4.5 % (n=15) vs SH: 51±4.3 % (n=16). Our data shows that the neuron-astrocyte interaction at NTS of mice, via GLT-1 activity, is not affected by SH exposure. Considering that the increase in TS-evoked glutamatergic current observed after SH is not related to changes in astrocyte glutamate transporter activity or pre-synaptic glutamate release, we suggest that it is related to changes in post-synaptic mechanisms.

Disclosures: M.S. Luz: None. **D. Accorsi-Mendonca:** None. **B.H. Machado:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.27/B97

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

Support: NIH Intramural Research Program

Title: Proximity labeling-based mapping of the EAAT3 interactome and identification of C-terminal interacting partners

Authors: *S. RADHAKRISHNAN[1], S. G. AMARA[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Natl. Inst. of Mental Hlth., NIMH, Bethesda, MD

Abstract: Plasma membrane neurotransmitter transporters clear neurotransmitters from the extracellular space and play a key role in regulating neuronal signaling. The neuronal excitatory amino acid transporter 3, EAAT3, is essential for glutamate clearance and modulation of glutamatergic tone. EAAT3 also transports cysteine into the cell where it serves as a rate-limiting substrate for the synthesis of glutathione, a key neuronal antioxidant. EAAT3 mutations are associated with several neuropsychiatric disorders such as schizophrenia and obsessive-compulsive disorders that may be due to its role in glutamate or cysteine transport. The activity of plasma membrane transporters can be altered by changes in transport kinetics, expression levels and trafficking to and from the plasma membrane. The C-terminus of EAAT3, specifically the ^{504}VNGGF^{508} motif is important for trafficking and the somatodendritic targeting of EAAT3 in hippocampal neurons. We had previously identified proteins interacting with purified GFP-EAAT3 wild-type (WT) and GFP-EAAT3 (504-509 AAAAAA) from rat brain lysates using a mass spectrometry (MS) based proteomics approach. We have now used the proximity labeling technique, TurboID to complement the results of classic affinity purification/MS-based interactome mapping and to capture transient interactions with endogenous proteins. The studies were conducted in Neuro2A cell line and primary cortical neuronal cultures with the TurboID tag expressed on EAAT3 WT or C- terminal mutants of EAAT3 with a cytosolic TurboID construct used as a spatial control. The TurboID tag covalently labels EAAT3 adjacent proteins in a proximity-dependent manner. The biotinylated proteins were enriched using streptavidin beads and identified by label-free mass spectrometry quantification. Pathway analysis of the proximity labeled proteins, identified pathways involved in regulation and signaling by Rho GTPase and membrane trafficking. Our comprehensive analysis of the EAAT3 interactome network will help us gain insights into the regulation and localization of the glutamate transporter in neurons.

Disclosures: S. Radhakrishnan: None. **S.G. Amara:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.28/B98

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

Support: National Science and Technology Council, Taiwan, Grant No. 110-2311-B-002-012
The Center for Advanced Computing and Imaging in Biomedicine, NTU-113L900703)

Title: Glutamate gradually elevates $[Zn^{2+}]_i$ via the CaM−CaMKII−NOS cascade in primary cultured rat embryonic cortical neurons

Authors: *C.-Y. PAN, H.-C. TSENG;
Natl. Taiwan Univ., Taipei, Taiwan

Abstract: <META NAME="author" CONTENT="建源 潘">
Zn^{2+} is pivotal for signaling in neuronal regulation, yet imbalance can cause cell death and neurodegenerative disorders. The intricate buffering system maintains low cytosolic Zn^{2+} concentration ($[Zn^{2+}]_i$), but details on physiological stimuli elevating $[Zn^{2+}]_i$ for neuronal processes remain limited. Our previous reports have demonstrated that dopamine elevates $[Zn^{2+}]_i$ through the cAMP−NO signaling pathway to activate autophagy and inflammation in cultured neurons. In this study, we adopted the Zn^{2+} imaging technique to verify the mechanism of how glutamate elevated $[Zn^{2+}]_i$ in cultured cortical neurons and examined the inflammatory response. Our results showed that glutamate elevates the $[Zn^{2+}]_i$ with an EC_{50} of 7.07 ± 2.12 μM, activating the ionotropic glutamate receptors that induced this elevation. Inhibitors against calmodulin (CaM), CaM-dependent protein kinase II (CaMKII), and NO synthase (NOS) blocked the glutamate-induced Zn^{2+} response. Membrane depolarization induced by a High-K^+ buffer significantly elevated the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) but only slightly increased the $[Zn^{2+}]_i$ and NO production. In addition, glutamate stimulation transiently increased the phosphorylation level of NO synthase at Ser^{1417} in 15 min. The presence of Zn^{2+} chelator, TPEN, significantly suppressed glutamate-induced formation of inflammasomes. Therefore, these results indicate that glutamate-induced local increment in $[Ca^{2+}]_i$ via the ionotropic glutamate receptors activates the CaM–CaMKII–NOS complex to produce NO and elevate $[Zn^{2+}]_i$. The elevated $[Zn^{2+}]_i$ initiates the inflammation in cultured neurons. Henceforth, we demonstrate a novel Zn^{2+} signaling pathway during neurotransmission after glutamate depolarizes the membrane potential and elevates $[Ca^{2+}]_i$, indicating the involvement of Zn^{2+} in modulating the long-term synaptic plasticity.

Disclosures: C. Pan: None. **H. Tseng:** None.

Poster

PSTR440: Modulation of Neurotransmission

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR440.29/B99

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

Support: NIDA F30 NRSA

Title: What is role of the blood-brain barrier in glutamate transport?

Authors: *I. H. GARCIA-PAK, M. RODRIGUEZ, Y. SHAO, R. DANEMAN;
Univ. of California San Diego, LA JOLLA, CA

Abstract: Due to the need for glutamate balance in the brain, there exists mechanisms of neuronal and astrocytic uptake of glutamate to prevent damage to the brain. Recent findings from our lab may indicate that the blood-brain barrier (BBB), too, could play a part in this vital regulation. The BBB, the vasculature within the central nervous system (CNS), possesses specific properties that make it unique compared to the vasculature in the periphery. By comparing the transcriptome of the endothelial cells (ECs) in the CNS to the ECs in the periphery of mice, we identified a BBB-specific gene expression profile revealing a possible BBB role in glutamate balance. One gene that arose out of interest was a glutamate transporter, *slc1a1*. Having this gene so highly enriched in brain ECs leads us to ask if the BBB is important for glutamate regulation. I hypothesize that the BBB modulates glutamate levels in the brain by the uptake of excess glutamate. To investigate this question, we generated EC-specific knockout (EC-KO) of *slc1a1*. Interestingly, in a behavioral screen, the *slc1a1* EC-KO showed a deficit in some behaviors related to sociability and anxiety. Additionally, initial electroencephalogram experiments on the *slc1a1* EC-KO revealed possible increased spike activity in a region-specific manner. This suggests that the BBB may indeed play a function in excitability and neurotypical brain function via this glutamate transporter. These studies will shed light on if the BBB role in excitatory-inhibitory balance in the brain and normal physiology by regulating glutamate.

Disclosures: I.H. Garcia-Pak: None. **M. Rodriguez:** None. **Y. Shao:** None. **R. Daneman:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.01/B100

Topic: B.05. Synaptic Plasticity

Title: Miniaturized microscope for two-photon lifetime imaging reveals CaMKII Activation dynamics in freely behaving mice

Authors: *T. SALEMI, L. YAN, Y. NAKAHATA, X. LIU, Z. YE, R. YASUDA;
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Normal 0 false false false EN-US X-NONE X-NONE /* Style Definitions */ table.MsoNormalTable {mso-style-name:"Table Normal"; mso-tstyle-rowband-size:0; mso-tstyle-colband-size:0; mso-style-noshow:yes; mso-style-priority:99; mso-style-parent:""; mso-padding-alt:0in 5.4pt 0in 5.4pt; mso-para-margin-top:0in; mso-para-margin-right:0in; mso-para-margin-bottom:8.0pt; mso-para-margin-left:0in; line-height:107%; mso-pagination:widow-orphan; font-size:11.0pt; font-family:"Calibri",sans-serif; mso-ascii-font-family:Calibri; mso-

ascii-theme-font:minor-latin; mso-hansi-font-family:Calibri; mso-hansi-theme-font:minor-latin; mso-bidi-font-family:"Times New Roman"; mso-bidi-theme-font:minor-bidi;} Intracellular signaling plays a pivotal role in synaptic plasticity, learning, and memory. The absence of a tool capable of observing neuronal signal transduction with subcellular precision in animals freely navigating has significantly limited its understanding. Fluorescent resonance energy transfer (FRET) based biosensors combined with 2-photon fluorescence lifetime imaging (2pFLIM) offer a method to monitor intracellular protein dynamics within live brain tissue. Here, we developed a miniature 2-photon head-mounted microscope for conducting in vivo FRET-FLIM (mini-2pFLIM). Mini-2pFLIM is capable of imaging a field of view of 350um x 350um with subcellular resolution in freely moving animals at a speed of up to 40Hz while simultaneously performing fluorescence intensity and lifetime imaging without affecting the natural foraging behavior of the animal. An electrotunable lens enabled us to image the supragranular layers within a range of 250 um of depth. We transfected layer 2/3 pyramidal neurons in the mouse somatosensory cortex (S1) with an improved mEGFP-based FRET biosensor for CaMKII activity (2dvCamuiα). After opening a craniotomy and implanting the mini scope over S1, we were able to image CaMKII activity in dendritic spines for up to ~1 hour. We found that exposure to an enriched environment increased the activity of CaMKII in a subset of dendrites and spines in the S1 region of the mouse cortex. Our system holds promise for imaging the activity of a broad array of proteins during naturalistic behaviors in mice, potentially unveiling the intricate intracellular protein mechanisms governing neuronal plasticity.

Disclosures: T. Salemi: None. **L. Yan:** None. **Y. Nakahata:** None. **X. Liu:** None. **Z. Ye:** None. **R. Yasuda:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.02/B101

Topic: B.05. Synaptic Plasticity

Support: JST SPRING JPMJSP2135

Title: Phosphorylation-dependent clustering mechanism of CaMKII revealed by high-speed AFM

Authors: *T. SUZUKI[1], T. SUMIKAMA[2], H. MURAKOSHI[3], M. SHIBATA[2];
[1]Grad. Sch. of Frontier Sci. Initiative, Kanazawa Univ., Kanazawa, Japan; [2]NanoLSI, Nano Life Sci. Institute, Kanazawa Univ., Kanazawa, Japan; [3]Supportive Ctr. for Brain Res., Natl. Inst. For Physiological Sci., Okazaki, Japan

Abstract: Long-term potentiation (LTP) and long-term depression (LTD) are fundamental cellular mechanisms underlying learning and memory. Functional synaptic plasticity is associated with alterations in synaptic signaling, whereas spine structural plasticity involves

changes in the volume of the postsynaptic spine of excitatory neurons. At the molecular level, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) plays a pivotal role in both functional and spine structural plasticity. CaMKII is a highly abundant protein within the post-synaptic density (PSD), comparable to the cytoskeletal proteins. However, the biological significance of the high concentration of CaMKII in spines and its role in the mechanisms of spine structural plasticity remains unclear. Here, we employed high-speed atomic force microscopy (HS-AFM) [1] to visualize the molecular dynamics of CaMKIIα at the single-molecular level. HS-AFM revealed that CaMKIIα molecules interact with each other to form clusters. To quantify the strength of intermolecular interactions within the clusters, we calculated pair distribution function (PDF). Our results showed that CaMKIIα in the basal and the LTP-related phosphorylation (pT286) state forms clusters via weak intermolecular interactions. In contrast, CaMKIIα in the LTD-related phosphorylation state (pT286/pT305/pT306) did not form clusters and was a scattered distribution. Furthermore, analyses of the CaMKIIα clustering area indicated that clusters in the LTP-associated phosphorylation state form larger clusters than in the basal state. This suggests that CaMKIIα accumulates in the spine and contributes to the expansion of spine volume during LTP induction. On the other hand, we observed an increase in the motility or diffusion coefficient of CaMKIIα in the LTD-related phosphorylation state based on an analysis of the mean squared displacement. This increased motility of CaMKIIα potentially explains the spine volume shrinkage observed in LTD. [1] S. Tsujioka *et al*. “Imaging single CaMKII holoenzymes at work by high-speed atomic force microscopy.” ***Sci. Adv.*** 9 (26), eadh1069 (2023).

Disclosures: T. Suzuki: None. **T. Sumikama:** None. **H. Murakoshi:** None. **M. Shibata:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.03/B102

Topic: B.05. Synaptic Plasticity

Title: Lactate enhances NMDA receptor responses through a mechanism requiring redox-sensitive interactions between GluN2B and CaMKII

Authors: G. HERRERA-LÓPEZ, H. FIUMELLI, *P. J. MAGISTRETTI;
BESE, King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Astrocyte-derived lactate not only fulfills the high energy demands of neurons but also acts as a neuromodulator that enhances neuronal plasticity and supports memory formation and consolidation. Lactate is known to influence neuronal excitability and regulate gene expression linked to neuroprotection and synaptic plasticity, but the pathways through which lactate operates still remain unclear. Here, we used patch-clamp recordings to demonstrate that lactate increases the amplitude and inactivation time constant of NMDA receptor (NMDAR) currents induced by glutamate and glycine. Not reproduced by HCAR1 agonists, this modulation

is dependent on monocarboxylate transporters and lactate dehydrogenase, indicating the requirement for lactate entry and metabolic conversion within neurons. Disruption of intracellular calcium dynamics or inhibition of CaMKII, a kinase linking Ca^{2+} to LTP, significantly diminishes the effects of lactate on NMDAR currents. We identified two potential redox-sensitive cysteine-containing sequences in the intrinsically disordered C-terminal domain of the GluN2B subunit that may play a role in the potentiation of NMDAR by lactate. In a compelling set of experiments in HEK cells, we observed that the presence of functional CaMKII and GluN2B-containing NMDARs is necessary for the lactate-enhancing effects. Mutations in GluN2B that prevent CaMKII binding and redox regulation via cysteines also prevent lactate's modulatory action. Quantitative immunoprecipitation experiments in neurons confirm that lactate increases the association between CaMKII and GluN2B. This interaction is crucial for the potentiation of NMDAR responses by lactate. Collectively, these results highlight a mechanistic pathway whereby lactate boosts NMDAR function through intracellular metabolic conversion and redox-sensitive interactions requiring CaMKII, establishing a link between metabolism and synaptic modulation in neurons.

Disclosures: G. Herrera-López: None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.04/B103

Topic: B.05. Synaptic Plasticity

Support: R37 MH057068 (T.C.S.)
R01 MH115304 (T.C.S., A.A.F.)
Downstate Seed Grant (T.C.S.)

Title: Double knockout of PKMζ and PKCι/λ eliminates late-LTP, indicating the atypical PKCs exclusively sustain late-LTP maintenance

Authors: *P. TSOKAS[1], C. HSIEH[2], D. A. CANO[3], A. B. GRAU-PERALES[6], R. E. FLORES-OBANDO[2], H. J. SMITH[7], Q. CHEN[3], K. D. ALLEN[8], J. E. COTTRELL[4], A. A. FENTON[6], T. C. SACKTOR[5];
[1]Physiol. & Pharmacology; Anesthesiology; The RF Furchgott Ctr. for Neural and Behavioral Sci., [2]Physiol. and Pharmacology; The RF Furchgott Ctr. for Neural and Behavioral Sci., [3]Sch. of Med., [4]Anesthesiol., [5]Physiol. & Pharmacology; Neurology; Anesthesiol; The RF Furchgott Ctr. for Neural and Behavioral Sci., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [6]Ctr. for Neural Sci., New York Univ., New York, NY; [7]Rutgers Grad. Sch. of Biomed. Sci., Highland Park, NJ; [8]Medgar Evers Col., Brooklyn, NY

Abstract: PKMζ is essential for maintaining late-LTP and long-term memory in wild-type (WT) mice, and PKCι/λ redundantly compensates for these fundamental processes in ζ-null mice

(Tsokas et al., doi.org/10.7554/eLife.14846). Conversely, PKCι/λ mediates early-LTP and short-term memory in WT mice, and PKMζ compensates for these processes in PKCι/λ knock-down mice (Sheng et al., doi.org/10.1093/cercor/bhx077) (PKCι/λ-null mice are embryonically lethal). To examine potential compensation by other PKCs that also increase in PKMζ-null mice, we first examined conditional PKMζ-KO (cPKMζ-KO) mice. We then eliminated both atypical PKC (aPKCs) by conditional knockout of PKCι/λ in hippocampus of PKMζ-null mice to examine functional compensation by other PKCs. **Methods:** cPKMζ-KO: CaMK2-CreERT2Prkczfl/fl mice received either systemic administration of 4-OH tamoxifen (TAM) or vehicle to activate Cre and delete the Prkcz gene in excitatory CaMKII-expressing cells. After 4-6 weeks, active place avoidance training was performed, and 1 week later brains were processed for IHC. Double aPKC-KO: AAV-Cre was injected in one hippocampus of PKCι/λ-floxed/PKMζ-null mice, and AAV-eGFP as control in the contralateral hippocampus. After 3 weeks, L-LTP was induced in CA1 st. radiatum. **Results:** In cPKMζ-KO mice, genetic deletion of Prkcz was compensated by upregulated PKCι/λ. PKMζ expression in cell bodies and dendritic compartments was reduced by TAM, as expected. PKCι/λ was strongly increased in cell bodies and also in dendrites, where it is detected only at low levels in WT mice. Vehicle vs. TAM, n's=4, t tests: $t6 < 4.7$, **P's < 0.003. In double aPKC-KO, the hippocampus with both aPKCs deleted shows diminished early-LTP and no L-LTP. Two-way repeated measures ANOVA revealed main effects of drug (AAV-Cre and AAV-eGFP, $F1,20 = 8.45$, $P = 0.0009$, $\eta 2p = 0.30$), and treatment (tetanization and sham, $F1,20 = 5.90$, $P = 0.025$, $\eta 2p = 0.23$), as well as 3-way interaction among drug x treatment x time (5-min average of pre-HFS and 3 h post-HFS, $F1,20 = 12.68$, $P = 0.002$, $\eta 2p = 0.39$). Tukey post hoc analysis confirms that, in contrast to AAV-eGFP-injected hippocampi ($P = 0.0004$), L-LTP was not maintained in AAV-Cre-injected hippocampi ($P = 0.99$, between baseline and 3 h post-HFS); n's = 6. **Conclusion:** WT mice show high levels of PKMζ in synapses and dendrites during memory storage, and PKCι/λ only low levels. In contrast, cPKMζ-KO mice, like PKMζ-null mice, compensate by persistently increasing PKCι/λ in synaptodendritic regions during spatial memory storage. Genetic deletion of both PKCι/λ and PKMζ shows no L-LTP, indicating no additional L-LTP maintenance mechanisms.

Disclosures: P. Tsokas: None. **C. Hsieh:** None. **D.A. Cano:** None. **A.B. Grau-Perales:** None. **R.E. Flores-Obando:** None. **H.J. Smith:** None. **Q. Chen:** None. **K.D. Allen:** None. **J.E. Cottrell:** None. **A.A. Fenton:** None. **T.C. Sacktor:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.05/B104

Topic: B.05. Synaptic Plasticity

Support: National Research Foundation of Korea: NRF-2018R1A2B6004759
National Research Foundation of Korea: NRF-2020R1A5A1019023
National Research Foundation of Korea: NRF-2022R1A2C1004913

Korea Dementia Research Project through the KDRC: HU21C0071
SNU CDMC 10-10 Project

Title: SHP2 regulates GluA2 tyrosine phosphorylation required for AMPA receptor endocytosis and mGluR-LTD

Authors: S. LEE[1,2], **J. KIM**[1,2], H.-H. RYU[3,2], Y.-S. LEE[3,2], *Y. SUH[2,1];
[1]Dept. of Biomed. Sci., [3]Dept. of Physiol., [2]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Post-translational modifications regulate the properties and abundance of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors that mediate fast excitatory synaptic transmission and synaptic plasticity in the central nervous system. During long-term depression (LTD), protein tyrosine phosphatases (PTPs) dephosphorylate tyrosine residues in the C-terminal tail of AMPA receptor GluA2 subunit, which is essential for GluA2 endocytosis and group I metabotropic glutamate receptor (mGluR)-dependent LTD. However, as a selective downstream effector of mGluRs, the mGluR-dependent PTP responsible for GluA2 tyrosine dephosphorylation remains elusive at Schaffer collateral (SC)-CA1 synapses. In the present study, we find that mGluR5 stimulation activates Src homology 2 (SH2) domain-containing phosphatase 2 (SHP2) by increasing phospho-Y542 levels in SHP2. Under steady-state conditions, SHP2 plays a protective role in stabilizing phospho-Y869 of GluA2 by directly interacting with GluA2 phosphorylated at Y869, without affecting GluA2 phospho-Y876 levels. Upon mGluR5 stimulation, SHP2 dephosphorylates GluA2 at Y869 and Y876, resulting in GluA2 endocytosis and mGluR-LTD. Our results establish SHP2 as a downstream effector of mGluR5 and indicate a dual action of SHP2 in regulating GluA2 tyrosine phosphorylation and function. Given the implications of mGluR5 and SHP2 in synaptic pathophysiology, we propose SHP2 as a promising therapeutic target for neurodevelopmental and autism spectrum disorders.

Disclosures: S. Lee: None. **J. Kim:** None. **H. Ryu:** None. **Y. Lee:** None. **Y. Suh:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.06/B105

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI 19K22834
JSPS KAKENHI 21K19752
JSPS KAKENHI 23K18456
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Shimizu Foundation for Immunology and Neuroscience Grant
Brain Science Foundation

Title: Essential roles of ROS - 8-nitro-cGMP signals in long-term memory of motor learning and cerebellar synaptic plasticity

Authors: *S. KAKIZAWA, S. YANAI, S. ENDO;
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Abstract: Reactive oxygen species (ROS) is known to have harmful effects in organisms. In addition, recent studies have demonstrated expression of ROS synthases at various parts of the organisms and the controlled ROS generation, suggesting possible involvement of ROS signaling in physiological events of individuals. However, physiological roles of ROS in the CNS, including functional roles in higher brain functions or neuronal activity-dependent ROS production, remain to be elucidated. Here, we demonstrated involvement of ROS - 8-nitro-cGMP signals in motor learning and synaptic plasticity in the cerebellum. In the presence of inhibitors of ROS signal or ROS synthases, cerebellar motor learning was impaired, and the stimulus inducing long-term depression (LTD), cellular basis for the motor learning, failed to induce LTD but induced long-term potentiation (LTP)-like change at cerebellar synapses. Furthermore, an imaging study revealed that ROS was produced by LTD-inducing stimulus in enzyme-dependent manner. Furthermore, as a downstream signal, involvement of 8-nitro-cGMP in motor learning and cerebellar LTD were also revealed. These findings indicate that ROS - 8-nitro-cGMP signaling is activated by neuronal activity and is essential for cerebellum-dependent motor learning and synaptic plasticity, demonstrating involvement of the signal in physiological function of brain systems.

Disclosures: S. Kakizawa: None. **S. Yanai:** None. **S. Endo:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.07/B106

Topic: B.05. Synaptic Plasticity

Support: NIH DSPAN RFA-NS-21-012

Title: Postsynaptic Function of cAMP Degrading Phosphodiesterase PDE4A5 in Modulation of AMPA Receptors

Authors: *Z. M. ESTRADA-TOBAR[1], C. MEYER[2], M. C. HORNE[1], J. W. HELL[3];
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Abstract: Signaling mediated by cyclic adenosine monophosphate (cAMP) is pivotal in synaptic plasticity and memory consolidation within the brain. The intricate orchestration of molecular events involves the formation of a distinctive signaling complex featuring the β2-adrenergic receptor (β2AR) alongside α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), Gs proteins, adenylyl cyclase (AC), and cAMP-dependent kinase (PKA). Upon stimulation by norepinephrine (NE), β2AR initiates a cascade culminating in the phosphorylation of the AMPAR GluA1 subunit at serine 845 (S845), thereby facilitating the trafficking of AMPARs to the postsynaptic membrane. This process is critical in long-term potentiation (LTP) of synaptic transmission induced by weak stimuli, which is a fundamental mechanism underlying learning and memory. Phosphodiesterases are critical for spatial restriction of cAMP signaling by hydrolyzing cAMP. Notably, sleep deprivation triggers upregulation of PDE4A5, impairing hippocampal LTP and resulting in memory consolidation deficits in a rodent. Thus, manipulating PDE4A5 presents a promising avenue for alleviating cognitive deficits associated with brain disorders. We identified a specific protein-protein interaction between PDE4A5 and the Src homology 3 (SH3) domain of postsynaptic density protein 95 (PSD-95), an essential anchor protein for AMPARs. With PSD-95 serving as a crucial organizer of synaptic structure, understanding the functional implications of PDE4A5 binding to its unique ~100 amino acid long N-terminus (NT) holds immense significance. Since the precise functional role of PDE4A5 and its association with PSD-95 is implicated in the trafficking of AMPA receptors, elucidating this relationship expands our understanding of fundamental brain processes. Moreover, it offers promise for developing targeted therapeutic interventions for cognitive disorders, particularly those associated with sleep deprivation and memory consolidation.

Disclosures: Z.M. Estrada-Tobar: None. **C. Meyer:** None. **M.C. Horne:** None. **J.W. Hell:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.08/B107

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01MH112151
NIH Grant U01DA056556
SFARI Pilot Award
SynGAP Research Fund

Title: Non-canonical splicing of SYNGAP1 regulates seizure susceptibility

Authors: *I. HONG[1], Y. HAN[1], Y. ARAKI[1], B. A. CLARKE[1], J. P. LING[2], R. C. JOHNSON[1], S. LEE[1], S. SRIPATHY[6], G. SHIM[7], S. MYUNG[3], Z. ZHANG[2], C. WILKS[4], S. SUN[2], B. J. MAHER[7], B. LANGMEAD[4,5], R. L. HUGANIR[1];
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Sci., Johns Hopkins Univ., Baltimore, MD; [6]Lieber Inst. For Brain Develop., Baltimore, MD; [7]Lieber Inst. for Brain Develop., Baltimore, MD

Abstract: *SYNGAP1* haploinsufficiency is a leading cause of intellectual disability, epilepsy, and autism. SYNGAP1 is the third most abundant protein in the post-synaptic density (PSD) and plays a critical role in NMDA receptor/CaMKII-dependent synaptic plasticity. A PDZ ligand unique to the α1 SYNGAP1 C-terminal isoform allows for interaction with PSD-95 at the PSD and is crucial for its role in synaptic plasticity. Here we find that the *SYNGAP1* α1 isoform arises from a GG-AG non-canonical splicing event unique to the brain and conserved across many mammalian species. The non-canonical splice donor site is a single base upstream of the α2 canonical GT splice donor and introduces a frameshift in the resulting C-terminal protein sequence of SYNGAP1, which encodes a PDZ ligand. A trichromatic *SYNGAP1* minigene splice reporter facilitated base-level interrogation of this splice junction and provided a means to screen antisense oligonucleotides (ASOs) that modulate alternative splicing. Systematic deletions within introns of the splice reporter revealed that *SYNGAP1* non-canonical splicing requires a well-conserved region spanning the first 40 bases of the intron following the splice donor. Further single nucleotide deletions and mutations established a critical role for the splice donor region (-4 to +3) and identified crucial bases in the intron necessary for α1 splicing. ASO screening on the minigene reporter led to several splice-switching ASOs that significantly increased (or decreased) α1 splicing. The top ASO candidate enhanced α1 expression in human iPSC-derived neurons in a dose-dependent manner, suggesting a novel therapeutic strategy for haploinsufficient individuals based on increasing this key *SYNGAP1* isoform while avoiding overt overexpression. A splice donor site mutation introduced into mice eliminated α1 splicing, leading to an α1 isoform knockout mouse line. Mice homozygous of this allele displayed substantially increased seizure susceptibility similar to heterozygous *Syngap1* knockout mice, indicating that the α1 isoform is critical for Syngap1 function and protection against seizure susceptibility. These findings illuminate a rare but highly conserved, brain-specific splicing mechanism that governs synaptic plasticity, and pave the way for a promising therapeutic approach for neurodevelopmental disorders achieved through modulation of non-canonical splicing.

Disclosures: I. Hong: None. **Y. Han:** None. **Y. Araki:** None. **B.A. Clarke:** None. **J.P. Ling:** None. **R.C. Johnson:** None. **S. Lee:** None. **S. Sripathy:** None. **G. Shim:** None. **S. Myung:** None. **Z. Zhang:** None. **C. Wilks:** None. **S. Sun:** None. **B.J. Maher:** None. **B. Langmead:** None. **R.L. Huganir:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.09/Web Only

Topic: B.05. Synaptic Plasticity

Support: NIH MH115456

Title: Syngap in the postsynaptic density

Authors: *T. MASTRO[1], C. LOPEZ[1], E. BUSHONG[2], R. NIETO[1], M. B. KENNEDY[1];
[1]Caltech, Pasadena, CA; [2]Michigan State Univ., Grand Rapids, MI

Abstract: SynGAP is a notable RAS GTPase activation protein in the postsynaptic density. SynGAP's role in fine-tuning excitatory and inhibitory balance has implications for neurological disorders such as autism spectrum disorder and epilepsy. It has long been considered integral to synaptic plasticity through its enzymatic activity, modified based on synaptic activity-dependent phosphorylation of critical residues. However, recent discoveries in our lab, affirmed by others, demonstrate a role in structural modulation of the postsynaptic density during long-term potentiation[1]. Using an in vitro primary neuron cell culture model, we demonstrate the critical role of synGAP as a placeholder for postsynaptic density. We confirm that synGAP regulates downstream signaling pathways for synaptic transmission through modulating Ras and Rap activity; however, its interaction with PSD-95 stabilizes synaptic components and mediates a competitive environment for binding in the postsynaptic density. 1. Araki Y, Rajkovich KE, Gerber EE, et al. SynGAP regulates synaptic plasticity and cognition independently of its catalytic activity. *Science*. 2024;383(6686):eadk1291. doi:10.1126/science.adk1291

Disclosures: T. Mastro: A. Employment/Salary (full or part-time):; University of Southern California. **C. Lopez:** None. **E. Bushong:** None. **R. Nieto:** A. Employment/Salary (full or part-time):; Bionano. **M.B. Kennedy:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.10/B108

Topic: B.05. Synaptic Plasticity

Support: NCBS-TIFR/DAE Proj. Id. No. RTI 4006
DBT/2018/NCBS/998
CEFIPRA/IFCPAR Project NO. 68T08-3

Title: A synaptic signaling atlas for pathway dynamics of ~1000 proteins in response to multiple ligands: experimental database and models

Authors: *U. S. BHALLA[1], A. BHATTACHARYA[2], T. DAS[1], M. N. DSOUZA[1], H. GUBBI VANI[1], R. MUDDASHETTY[3], N. A. VISWAN[1];
[1]Natl. Ctr. For Biol. Sci., Bangalore, India; [2]Ctr. for Brain Develop. and Repair, Instem-Ncbs, Bengaluru, India; [3]Ctr. for Brain Res., IISc., Bangalore, India

Abstract: Synaptic function and dysfunction emerge from complex signaling networks which underlie activity-driven growth, plasticity, protein turnover, and sometimes loss of synapses. Proteomics studies have given a sense of the enormous number of participating pathways but not

their dynamics over short-time-scales (<=30 min) during which many key signaling events occur. We employed unbiased phosphoproteomics, and targeted proximity ligase assays to obtain time-series readouts of synaptic signaling responses to a suite of ligands. In our first-pass assays we measured signaling in mouse P30 hippocampal synaptoneurosomes following application of one of NMDA, DHPG, ACh, NE, 5HT, EGF, or BDNF. We standardized sample preparation and mass-spectrometry protocols for quantitative unbiased monitoring of around 1000 phosphoproteins. We validated individual readouts from the obtained phosphoprotein time series against selected Western blots. We used this dataset to parameterize synaptic signaling models at four different levels of granularity, from highly reduced to full ODE-stochastic models with thousands of molecular species. To do this, each stimulus-response experiment in the database was encoded in a standard experiment-specification format, (FindSim, https://findsim.ncbs.res.in/) and the database of experiments was used to feed a model optimization pipeline (HOSS, https://github.com/BhallaLab/HOSS). These standardized assays open the way to systematically measure synaptic signaling from different brain regions, multiple age-points, and from mouse and human models of neurodevelopmental and neuropsychiatric disease. We have used it to build a family of healthy and disease synaptic signaling models. Our first release of this dataset is for the control (WT) P30 mouse hippocampus. Samples have been banked for cortex and striatum at P30 and P60 for wild-type, and Familial Alzheimer Disease (FAD) mutant mouse lines. The resultant multidimensional dataset and models form the basis for a synaptic signaling atlas in health, aging, and disease.

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Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.11/B109

Topic: B.05. Synaptic Plasticity

Support: NS104705
1456818
MH116003
NS118731

Title: Elucidating the role of glutamate delta-1 receptor (GluD1) in protein kinase c (PKC) dependent synaptic plasticity in the dorsal striatum

Authors: *P. CHETTIAR[1], S. DRAVID[2];
[1]Psychiatry and Behavior Sci., Texas A & M Univ., College Station, TX; [2]Texas A & M Univ., College Station, TX

Abstract: Synaptic plasticity, essential for learning and memory, involves modifying synaptic strength, guidedby the enzyme Protein Kinase C (PKC). While PKC's role in various brain regions is well-documented,its function in the striatum a critical area for motor and reward processes is less understood. Thisstudy focuses on the glutamate delta-1 receptor (GluD1) in the striatum, investigating itscontribution to PKC-driven synaptic plasticity, particularly as it contrasts with the established role ofthe glutamate delta-2 receptor (GluD2) at the Purkinje cell-to-parallel fiber synapse.Using brain slice electrophysiology, we found PKC activation alters NMDA receptor responses in thedorsal striatum, manifesting as depression rather than the typical potentiation observed elsewhere.This effect relies on GluD1, as shown by reduced responses in GluD1 knockout models.Consequently, we developed peptides mimicking this unique GluD1-dependent modulation, which,when applied to the dorsal striatum, improved cognitive flexibility and motor learning, indicatingpotential therapeutic applications.
Our research unveils a novel synaptic plasticity form, emphasizing GluD1's specific role through PKCactivation in the dorsal striatum. This advances our understanding of synaptic regulation andsuggests new treatment avenues for neuropsychiatric conditions, highlighting the brain's synapticcomplexity and specificity.

Disclosures: P. chettiar: None. **S. Dravid:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.12/B110

Topic: B.05. Synaptic Plasticity

Support: NIH Grant NS084111
NIH Grant NS114914
NIH Grant NS119512

Title: The scaffold Scribble regulates Rac1 activity during LTD

Authors: *T. A. KHAN[1], L. CANCEDDA[2], M. SHELLY[1];
[1]Stony Brook Univ., Stony Brook, NY; [2]Brain Develop. and Dis., Inst. Italiano di Tecnologia, Genova, Italy

Abstract: The RhoGTPase Rac1 is a major regulator of the actin cytoskeleton in dendritic spines. Spines serve as the functional receivers of synaptic input where the reorganization of spine actin cytoskeleton underlies the functional outcomes of synaptic plasticity such as AMPAR trafficking and spine remodeling. Intriguingly, recent evidence suggests that Rac1 is a critical regulator of both forms of synaptic plasticity, LTP and LTD. LTP is triggered by a strong but brief stimulus, resulting in the addition of AMPARs to the synaptic surface and an increase in spine size. In contrast, LTD, is initiated by a weak and prolonged stimulus, reducing the number of GluA2 containing AMPARs and shrinking the spine size. However, what determines Rac1

activity towards one form of plasticity over the other remains largely unknown. Historically, Rac1 has primarily been linked to LTP, with few studies investigating its involvement in LTD. Rac1 requires activation by guanine nucleotide exchange factors (GEFs) that catalyze the GDP to GTP exchange of Rac1-bound GDP to Rac1-bound GTP. Many Rac1 GEFs are intimately associated with LTP but few with LTD. Here we reveal that Rac1 is a significant regulator of LTD and is its function is facilitated by the scaffold protein Scribble by forming a signaling complex with a Rac1 GEF. Scribble is a multidomain signaling organizer that can interact with a plethora of proteins to conduct distinct signaling pathways. We hypothesize, Scribble regulates Rac1 activity during LTD via a Rac1 GEF and is critical for GluA2 containing AMPAR endocytosis and actin remodeling.

Disclosures: T.A. Khan: None. **L. Cancedda:** None. **M. Shelly:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.13/B111

Topic: B.05. Synaptic Plasticity

Support: R01 NS115776

Title: Lrrc57 is an evolutionarily conserved pre-synaptic modulator of neurotrophin signaling

Authors: *D. GARIC[1], J. G. MURPHY[2], C. M. DAVENPORT[1], B. J. TEUBNER[1], S. ZAKHARENKO[3];
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Abstract: Bipolar Disorder (BD) is a complex polygenic mental disorder associated with dramatically increased risk of suicide and is characterized by recurrent episodes of mania and depression. *LRRC57* is a gene/protein of unknown function that has been implicated through several genome-wide association and transcriptomic studies in the etiology of BD. The *Lrrc57* gene encodes a 27 kDa horseshoe-shaped protein which belongs to the class of **L**eucine-**R**ich **R**epeat domain **C**ontaining proteins. It displays high degree of evolutionary conservation across all *Metazoa,* its expression is highly enriched in the neurons of *D. melanogaster* and *C. elegans* and its deletion in these organisms is lethal. In order to investigate the biological function of LRRC57 gene/protein, we created a monoclonal antibody and mouse models for its germline and conditional deletion/overexpression. We demonstrated that LRRC57 is a novel protein highly expressed in the excitatory neurons of the cortex and CA3 area of the hippocampus. Germline deletion of Lrrc57 in mice results in fully penetrant embryonic lethality by E18.5. Early conditional deletion ($Emx1^{Cre};Lrrc57^{flox/flox}$) leads to cortical and hippocampal neurodegeneration in about 50% of mice, increased frequency of spontaneous EPSC (sEPSC) and hyperactivity in

the open field test. Late onset deletion of Lrrc57 in the excitatory neurons (*CaMKIIα^{Cre};Lrrc57$^{flox/flox}$*) leads to the increase in the frequency of sEPSC as well as impairment in short- and long-term memories without any visible morphological changes. Ectopic overexpression of Lrrc57 strongly increases the growth of neurite-like extensions in PC12 cells in response to NGF, whereas CRISPR/Cas9-mediated KO of Lrrc57 in 661W cells decreases their proliferation rate in response to bFGF. Lrrc57 KO does not alter the growth of neurite-like extensions in PC12 cells nor Lrrc57 OE affects the rate of 661W proliferation in response to growth factors. These results suggest cell type-specific roles in modulating cellular responses to growth factors. Finally, examination of the activity of Ras/MAPK pathway by Western blot in 661W cells reveals hypo- and hyper-activation of this signaling cascade upon Lrrc57 KO and OE respectively. In conclusion, Lrrc57 is a novel, evolutionarily conserved modulator of neurotrophic growth factor signaling, which is required for the survival of cortical and hippocampal neurons, synaptic plasticity and cognitive function.

Disclosures: D. Garic: None. **J.G. Murphy:** None. **C.M. Davenport:** None. **B.J. Teubner:** None. **S. Zakharenko:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.14/B112

Topic: B.05. Synaptic Plasticity

Support: NIH NS111986

Title: Differential contribution of BDNF-TrkB signaling to hippocampal synaptic plasticity

Authors: J. RAINGO, F. LEMTIRI-CHLIEH, *E. LEVINE;
Univ. of Connecticut Sch. of Med., Farmington, CT

Abstract: The goal of these studies is to explore the role of brain-derived neurotrophic factor (BDNF) in regulating activity-dependent synaptic plasticity in the hippocampus. BDNF has been implicated in a diverse range of physiological processes, including sensory perception, motor coordination, memory, and cognitive abilities. Disruption of BDNF signaling may play a role in several neurologic and psychiatric disorders, including anxiety, depression, schizophrenia, and seizure disorders, and this neuromodulatory system is currently a major target for the development of novel therapeutics. In the present studies, we examined the role of BDNF in various forms of log-term potentiation (LTP) by recording field excitatory postsynaptic potential (fEPSPs) in the CA1 stratum radiatum in hippocampal slices from juvenile mice. LTP was induced electrically using either theta-burst stimulation (TBS) or high-frequency stimulation (HFS). LTP was also induced pharmacologically using a cocktail containing forskolin and rolipram in low Mg, which increases intracellular cAMP and enhances NMDA receptor activation. Significant LTP (~50% increase from baseline for greater than 1 hour) was induced

by either one or three trains of TBS. This potentiation was completely blocked by an NMDA receptor antagonist, and was significantly inhibited by preventing TrkB receptor activation with the antagonist ANA-12. TBS-induced LTP was inhibited to a similar extent by the trk tyrosine kinase inhibitor K252a. The effect of TrkB antagonism on TBS-LTP was still observed in the presence of the GABA-A receptor antagonist picrotoxin, suggesting that endogenous BDNF may enhance LTP by acting directly on glutamatergic synapses. Similarly, chemically-induced LTP also required endogenous BDNF and TrkB signaling because it was inhibited by ANA-12 or K-252a. In contrast, HFS (100 Hz/1 sec) induced LTP that was not affected by TrkB receptor antagonism, indicating a differential role for endogenous BDNF depending on the induction paradigm.

Disclosures: J. Raingo: None. **F. Lemtiri-Chlieh:** None. **E. Levine:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.15/B113

Topic: B.05. Synaptic Plasticity

Support: NIH Grant

Title: Estradiol Signalling Pathways Mediating Sex Differences In Striatal Synaptic Plasticity

Authors: *V. MALLYA;
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Abstract: ***Estradiol Signaling Pathways Mediating Sex Differences in StriatalSynaptic Plasticity.***Striatal Synaptic Plasticity is key to our understanding of reward learning and habit formation.Estradiol ,a female sex hormone that is elevated during estrus,has been shown to impair LTP in the DMS of female mice.However, the mechanisms underlying this impairment are unclear. In adult mice, estradiol works through two estradiol receptors in the membrane: ERα and GPER.To understand estradiol's role in impairing striatal synaptic LTP we created a D1 spiny projection neuron (SPN) signalling pathway model with synaptic activation of ERK, protein kinase A, protein kinase C, CaMKII and the endocannabinoid 2AG as read-outs to assess LTP versus LTD. We simulated the model using our computationally-efficient stochastic reaction-diffusion simulator, NeuroRD.We investigated the effect of estradiol activation of ERα receptors (which are coupled with mGlur5[Gq coupled] and mGlur3[Gi coupled] receptors) and GPER(Gs coupled). Our preliminary simulation results show that mGluR5 activation does not lead to a change in ERK activation ,but instead increases the concentration of 2-AG, which is a key molecule for producing LTD.Further, stimulating with dopamine causes a slight reduction in ERK activation and an increase in 2-AG concentration.These findings indicate that LTD in D1 SPNs may be facilitated by estradiol acting through mGluR5.We also investigate the role of GPER which leads to production of cAMP, to determine whether this estradiol receptor also

impairs LTP. Finally, as the first multi-compartmental spatial model of ERK in the striatum, we will delve into the role of estradiol in subcellular localisation of ERK activity ,specifically investigating whether changes in ERK activity predominantly occurs in the spine or dendrite .

Disclosures: V. mallya: None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.16/B114

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

Support: MH122461
T32AA007583

Title: Astrocytic FABP5 Mediates the synaptic transport of Endocannabinoid at Hippocampal GABA Synapses

Authors: *S. OUBRAIM[1], M. FAUZAN[2], K. M. STUDHOLME[2], S. GLASER[3], R.-Y. SHEN[4], M. KACZOCHA[2], S. HAJ-DAHMANE[4];
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Abstract: Fatty acid binding protein 5, a protein chaperone that plays a central role in the regulation of lipid trafficking, including the endocannabinoids (eCBs) 2-arachidonoylglycerol (2-AG) and anandamide. We have previously shown that FABP5 is indispensable for retrograde eCB functions in the brain. However, the cellular origin and mechanisms by which FABP5 controls synaptic 2-AG signaling remain unknown. In this study, we employed electrophysiology, pharmacological, and genetic approaches to define the cellular origin and mechanisms by which FABP5 gates 2-AG signaling at hippocampal CA1 pyramidal neurons GABA synapses. Our results revealed that pharmacological inhibition and genetic deletion of FABP5 inhibited 2-AG-mediated depolarization-induced suppression of inhibition (DSI). In FABP5 KO mice, the DSI was readily rescued by AAV-mediated expression of FABP5, but not FABP7. The DSI was also rescued in FABP5 KO mice by AAV-mediated expression of a secreted variant of FABP5, but not by a mutant that does not bind to 2-AG, thereby indicating that FABP5 secretion and 2-AG binding is required for the signaling of DSI. Furthermore, using $FABP5^{Flox}$ mice, we found that conditional deletion of FABP5 in astrocytes, but not in neurons, blocked 2-AG mediated DSI, which was fully restored by AAV-mediated astrocytic expression of FABP5 in FABP5 KO mice. Together, these findings indicate that astrocytic FABP5 is a synaptic carrier that mediates the transport of 2-AG at central GABA synapses.

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Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.17/B115

Topic: B.05. Synaptic Plasticity

Support: Trond Mohn Foundation (TMS2021TMT04)
The Medical Student Research Programme at The Faculty of Medicine, University of Bergen

Title: Nanobody-based proximity ligation assay detects constitutive and stimulus-regulated native Arc oligomers in hippocampal neuronal dendrites

Authors: *H. FEVANG[1], R. DA SILVA MAZZARINI BALDINOTTI[1], F. P. PAUZIN[2], Y. ISHIZUKA[3], C. R. BRAMHAM[4];
[1]The Dept. of Biomedicine, Univ. of Bergen, Bergen, Norway; [2]Univ. of Bergen, The Department of Biomedicine, Norway; [3]Dept. of Pathoppysiol. & Metab., Kawasaki Med. Sch., Okayama, Japan; [4]Univ. of Bergen, N-5009 Bergen, Norway

Abstract: Activity-regulated cytoskeleton-associated (Arc) protein is a product of an immediate early gene (IEG) and involved in different forms of synaptic plasticity. The oligomeric state of Arc is hypothesized to modulate its function in these processes. In this study we developed a nanobody based method for detecting Arc-Arc self-association *in situ* in rat primary hippocampal neurons using proximity ligation assay (PLA). To detect the proximity between Arc molecules we used nanobodies with single, structurally defined Arc epitopes. C11 binds to the C-lobe of Arc's capsid domain, while H11 targets the hydrophobic ligand pocket of the N-lobe. Each of the nanobodies were ALFA- and FLAG-tagged, for use in either H11 or C11 based PLA. The method resulted in detection of widespread, punctate PLA signals in neuronal dendrites. To elucidate the nature of the Arc-Arc complexes, neuronal cultures were exposed to tetrodotoxin to inhibit neuronal firing activity or to cycloheximide to block protein synthesis. Neither treatment affected the PLA signal, suggesting that Arc-Arc complexes are stable and independent of recent neuronal activity and protein synthesis. Additionally, we exposed cultures to a cell-penetrating peptide inhibitor of Arc oligomers larger than dimers (OligoOFF peptide). H11 based PLA signal was reduced by the OligoOff treatment, while PLA signal detected by C11 was unaffected. Furthermore, we evaluated Arc complex formation in response to chemical stimuli that increases Arc synthesis. Brain-derived neurotrophic factor (BDNF) is known to increase expression of dimeric Arc, while (RS)-3,5-dihydroxyphenylglycine (DHPG) induces Arc synthesis, and endocytosis through higher-order Arc oligomers. We found that BDNF increased the abundance of PLA puncta detected by C11, but not H11. Conversely, only H11 PLA signal was increased after DHPG treatment. We propose that Arc oligomeric state affects the availability of epitopes

for binding. The results are consistent with preferential detection of Arc dimers by C11 and higher-order oligomers by H11. In sum, nanobody-based PLA reveals constitutive and stimulus-regulated native Arc oligomers in hippocampal neuronal dendrites.

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Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.18/B116

Topic: B.05. Synaptic Plasticity

Support: DA041711

Title: Gaq in primary sensory neurons promotes opioid-induced hyperalgesia and tolerance by potentiating NMDA receptor phosphorylation, interaction with a2d-1, and synaptic expression

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Abstract: 1
Opioids typically inhibit nociceptive transmission from primary sensory neurons to spinal dorsal horn neurons by activating Gαi/o-coupled μ-opioid receptors. By contrast, some Gαq-coupled receptors and NMDARs are implicated in opioid-induced hyperalgesia and analgesic tolerance. However, the potential role of Gαq proteins in opioid-induced NMDAR hyperactivity and associated hyperalgesia and tolerance remains enigmatic. In this study, we demonstrated that inhibiting Gαq with FR900359 reversed morphine treatment–augmented GluN1 serine phosphorylation, GluN1-α2δ-1 interactions, and their synaptic expression in rat spinal cord synaptosomes. FR900359 also abolished the increase in morphine treatment–induced presynaptic NMDAR activity, measured by mEPSCs and dorsal root–evoked monosynaptic EPSCs in spinal lamina II neurons. However, morphine treatment did not alter Gαq protein levels, and there was no direct interaction between Gαq and μ-opioid receptors in the dorsal root ganglion (DRG) or spinal cord. Furthermore, CRISPR/Cas9-induced conditional Gαq knockdown in DRG neurons of mice normalized morphine treatment–induced increases in GluN1-α2δ-1 interactions and their protein levels in spinal synaptosomes. Correspondingly, Gαq knockdown in DRG neurons abrogated NMDAR-mediated long-term potentiation elicited by μ-opioid receptor stimulation in spinal lamina II neurons. In addition, intrathecal injection of FR900359 in rats or conditional Gαq knockdown in DRG neurons in mice not only potentiated the acute analgesic effect of morphine but also attenuated morphine treatment–induced hyperalgesia and tolerance. Collectively, our findings suggest that via crosstalk between μ-opioid receptors and Gαq-

mediating signaling, opioid treatment enhances NMDAR phosphorylation, synaptic trafficking, and activity at primary afferent central terminals, thus perpetuating the development of hyperalgesia and tolerance.

Disclosures: D. Jin: None. **Y. Huang:** None. **H. Chen:** None. **S. Chen:** None. **H. Pan:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.19/B117

Topic: B.05. Synaptic Plasticity

Support: NIH: T32 MH016880
ABNexus Pilot Support Funding Program
NIH: R01 NS086933

Title: Cb1-receptor-dependent long-term depression is attenuated with the loss of akt1 and gabaergic akt1 activity mediates anxiety-like behavior in a sex-specific fashion

Authors: *M. GRIFFIOEN[1,2], C. BORSKI[1], J. HANSON[3], J. K. KUSHNER[4], C. HOEFFER, Jr.[3];
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Abstract: AKT is a central protein kinase essential to many different neuronal processes. AKT is present in most cell types in the brain, with three structurally similar isoforms (AKT1, AKT2, AKT3) encoded by distinct genes. AKT1 and AKT3 are expressed in excitatory neurons, with only AKT1 expressed in interneurons. Importantly, these isoforms have isoform and cell-specific roles in synaptic plasticity and sex-dependent effects on behavior. Because AKT function plays a role in memory formation and anxiety expression, AKT is implicated in many neurological disorders, such as Alzheimer's disease (AD), autism spectrum disorder (ASD), generalized anxiety disorder (GAD), and schizophrenia. Interneuronal dysfunction has been proposed to contribute to the pathophysiology of neuropsychiatric disorders, and the removal of *Akt1* alters anxiety-like behavior, extinction of learning, extinction of long-term memory (LTM), and renewal of extinguished memory, thus making it crucial to elucidate AKT1's function in interneuronal regulation. Using genetic mouse models that selectively remove AKT1 from interneurons, our studies revealed AKT1 interneuron-specific and sex-dependent effects on anxiety-like behaviors. Because endocannabinoid (eCB) signaling is known to modulate IN activity and affect behavior and fear extinction, we investigated eCB signaling in the context of AKT1 function. We found that cannabinoid receptor (CR) activation promoted AKT1 activation, *Akt1* deficiency altered CR-dependent signaling, and long-term depression (LTD) in a sex-specific manner. In addition, we found that CB1 activation on slices obtained from mice lacking

AKT1 expression in interneurons enhanced CR-dependent LTD. Using these genetic mouse models to interrogate the role of interneuronal AKT1 in neurological disorders, we will identify new therapeutic targets for treating and diagnosing diseases such as schizophrenia and AD. These data will also contribute valuable information about AKT1 function in the context of biological sex, a variable that plays a significant role in the manifestation of mental health disorders.

Disclosures: M. Griffioen: None. **C. Borski:** None. **J. Hanson:** None. **J.K. Kushner:** None. **C. Hoeffer:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.20/B118

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R35NS132349

Title: Regulation of hippocampal neuron excitability and synaptic transmission by the endoplasmic reticulum proteins STIM1 and STIM2

Authors: *K. S. KORSHUNOV, M. E. MARTIN, M. PRAKRIYA;
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Abstract: Ca^{2+} signaling regulates a wide range of cellular functions in the nervous system including gene transcription, vesicular exocytoisis, and membrane excitability. A widespread mechanism for mobilizing Ca^{2+} signals in most cells is store operated Ca^{2+} entry (SOCE). In this pathway, depletion of endoplasmic reticulum (ER) Ca^{2+} stores activates the ER Ca^{2+} sensors, stromal interaction molecules 1 and 2 (STIM1/STIM2) which then bind to and gate open the Orai family of Ca^{2+} channels to initiate Ca^{2+} influx into the cytosol. Previously, we found that the Ca^{2+} channel, Orai1, is critical for synaptically-evoked Ca^{2+} signals in dendritic spines of hippocampal neurons. These studies showed that Orai1 is essential for driving several steps of synaptic plasticity in dendritic spines and for induction of long-term potentiation (LTP) and for working and associative learning. However, the role of the STIM proteins for synaptic plasticity and cognitive fucntions has not been addressed. Here, we examined various aspects of synaptic transmission, membrane excitability, and synaptic plasticity in mice with conditional knockouts of STIM1 or STIM2 in excitatory neurons. Our results indicate that deletion of STIM1 or STIM2 did not impact basal excitatory and inhibitory synaptic transmission on CA1 hippocampal neurons. Whereas conditional deletion of STIM1 did not significantly affect membrane excitability, deletion of STIM2 significantly enhanced CA1 neuron action potential spiking and these mice also exhibited increases in LTP. Behavioral working and associative learning tests showed that deletion of STIM1 or 2 did not impair learning behaviors. These findings advance

our understanding of the roles of the STIM proteins in hippocampal neuron cell physiology and reveal potential differences between the phenotypes of the STIM1/2 and Orai1 knockout mice.

Disclosures: K.S. Korshunov: None. **M.E. Martin:** None. **M. Prakriya:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

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Program #/Poster #: PSTR441.21/B119

Topic: B.05. Synaptic Plasticity

Support: French Association France Alzheimer (AAPSM2018Dossier1795
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Agence Nationale de la Recherche (ANR-21-CE16-0032APPYSYNAPSE
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Title: APP fragment AETA controls both ionotropic and non-ionotropic signaling of NMDA receptors, which impacts Alzheimer's disease pathology

Authors: *J. DUNOT[1], H. MARIE[2];
[1]Inst. of Mol. and Cell. Pharmacol., valbonne, France; [2]Inst. de Pharmacologie Moleculaire et Celluaire (IPMC), Valbonne, France

Abstract: NMDA receptors (NMDARs) are ionotropic receptors crucial for brain information processing. Yet, evidence also supports an ion flux-independent signaling mode mediating synaptic long-term depression (LTD) and spine shrinkage. How these different modes of NMDAR activity are controlled remains unknown. Here, we identify AETA (Aη), an amyloid-β precursor protein (APP) cleavage product, as an NMDAR modulator with the unique dual regulatory capacity to impact both signaling modes. AETA inhibits ionotropic NMDAR activity, principally of GluN2A containing heteromers, by competing with the co-agonist and induces an

intracellular conformational modification of GluN1 subunits. This favors ion flux-independent NMDAR signaling leading to enhanced LTD, and spine shrinkage. Endogenously, AETA production is increased by *in vivo* chemogenetically-induced neuronal activity, suggesting that it can act as an activity-dependent modulator of NMDARs. Genetic deletion of the AETA production pathway in mice alters NMDAR transmission and prevents LTD, phenotypes rescued by acute exogenous application of AETA. This genetic deletion also impairs contextual fear memory formation, a phenotype rescued upon reintroduction of AETA in the brain *in vivo*. We asked whether AETA, due to its newfound role as a modulator of NMDARs, could be implicated in Alzheimer's disease (AD) aetiology. We quantified AETA levels in human prefrontal cortex and hippocampi of control and AD patients and observed that AETA accumulates in AD brains. To understand how this might perturb brain information processing, we generated a new mouse model, the AETA-m line, which harbors a chronic increase of the secreted human form of AETA in the brain. Behaviorally, these mice exhibit altered long-term spatial memory. These perturbations correlate with alterations of NMDAR activity and NMDAR-dependent synaptic plasticity. Our findings reveal AETA as a unique type of endogenous modulator of NMDARs, exerting bidirectional control over their signaling and associated brain information processing but also as a new contributor to several pathological features pertaining to AD.

Disclosures: J. Dunot: None. **H. Marie:** None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR441.22/B120

Topic: B.05. Synaptic Plasticity

Support: R01NS129198
R01NS099340
R01NS097498

Title: Dual roles of the SNX17-Retriever and SNX27-Retromer endomembrane recycling pathways in regulating synaptic function and plasticity in hippocampal neurons

Authors: *G. CHAVIS;
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Abstract: The insertion and removal of integral membrane proteins is a key mechanism for the regulation of synaptic function. Once surface proteins are internalized, they can either be routed to lysosomes for degradation or can be recycled back to the cell surface. Two recycling protein complexes - the SNX27-Retromer complex and the recently discovered SNX17-Retriever complex - are the main drivers in recycling internalized cargoes in non-neuronal cells. In neurons, the SNX27-Retromer pathway has been shown to regulate surface expression of AMPA-type glutamate receptors (AMPARs) during long-term potentiation (LTP), but the role of

the SNX17-Retriever pathway in synaptic function and plasticity remains poorly understood. Using cultured hippocampal neurons and hippocampal slices, we demonstrate that disruption of the SNX17-Retriever pathway leads to the functional and structural loss of excitatory synapses and impairs activity-dependent forms of synaptic plasticity. The similar role of SNX17-Retriever and SNX27-Retromer in Hebbian forms of plasticity such as LTP does not appear to reflect activity at the same cargoes, as preliminary studies suggest that SNX27 and SNX17 sort distinct cargos in neurons. Together, our results suggest that the SNX17-Retriever and SNX27-Retromer recycling pathways each play important, but unique, roles in maintaining and remodeling excitatory synapses.

Disclosures: G. Chavis: None.

Poster

PSTR441: LTP and LTD: Molecular Pathways and Signaling

Location: MCP Hall A

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Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01HL142129
NIH Grant HL142129-04S1
NIH Grant R01105588

Title: Protection of long-term memory storage mechanisms induced by a high-fat, high-cholesterol diet through genetic deletion of inflammatory transcription factor STAT4

Authors: *C. M. HOLLANDER[1], X.-L. ZHANG[1], M. D'SILVA[2], J. NADLER[3], P. K. STANTON[1];
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Abstract: Signal transducer and activator of transcription 4 (STAT4) is an inflammatory transcription factor that, upon activation, translocates to the nucleus and regulates the expression of genes essential for the differentiation of T-helper 1 cells, which play a vital role in immune responses. A high-fat, high-cholesterol diet (HFD-C) triggers interleukin-12 release, which activates STAT4 and contributes to the development of autoimmune and inflammatory diseases such as atherosclerosis, rheumatoid arthritis and diabetes-related cardiovascular inflammation. These conditions increase the risk of memory-related disorders like vascular dementia and Alzheimer’s disease. The specific mechanisms responsible for this increased risk remain unidentified. Two forms of activity-dependent long-term synaptic plasticity that play important roles in long-term memory storage, are activity-dependent long-term potentiation (LTP), which persistently strengthens synaptic connections after high-frequency stimulation, and long-term depression (LTD), which weakens the same connections after low-frequency stimulation. We assessed LTP and LTD at Schaffer collateral-CA1 synapses in acute hippocampal slices from

two strains of mice. One strain was a transgenic STAT4 knockout ($STAT4^{\Delta LysM}LDLr^{-/-}$), with reduced STAT4 expression in myeloid cells and neurons, while the other was a control strain from the same background ($Stat4^{fl/fl}LDLr^{-/-}$), with normal STAT4 expression. Mice were fed either a normal diet or a prolonged HFD-C for 16 weeks. Under normal dietary conditions, both strains exhibited similar profiles of paired-pulse facilitation, basal synaptic transmission, LTP and LTD at 3 and 24 weeks of age. However, after mice were fed a 16-week HFD-C diet, mice with normal STAT4 expression showed a significant decrease in LTP, while LTD was unaffected. In contrast, mice with reduced STAT4 expression were protected from HFD-C induced LTP impairment, exhibiting magnitudes of LTP comparable to control mice with normal STAT4 expression, while LTD was still unaffected. This suggests that STAT4 is a key mediator of HFD-C induced impairments in synaptic plasticity, and that suppression of STAT4 could mitigate the impact of an HFD-C diet on LTP, without affecting LTD. Given that HFD-C diets are associated with increased risk of both diabetes and Alzheimer's disease, STAT4 may be a key therapeutic target for reducing the risk of developing memory-related conditions like vascular dementia and Alzheimer's disease.

Disclosures: C.M. Hollander: None. **X. Zhang:** None. **P.K. Stanton:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.01/B122

Topic: B.07. Network Interactions

Support: DIRP, NIMH, USA, ZIAMH002797, ZIAMH002971
BRAIN initiative Grant U19 NS107464-01, ZIAMH00279

Title: One neuron, one vote: neuronal contributions to parabolic avalanche activity

Authors: *K. SRINIVASAN, T. L. RIBEIRO, D. PLENZ;
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Abstract: Neuronal avalanches—cascades of synchronized neural activity—are considered a key marker of criticality in superficial layers of the brain's cortex. Avalanches follow shallow power laws in terms of size and duration, supporting highly selective, system-spanning synchronization, considered to play a major role in information processing. However, their proper measurements have been difficult to achieve, particularly in the awake animal. We recently demonstrated that temporal coarse-graining establishes the range of spatiotemporal resolution at which parabolic avalanches are properly observed in vivo. Within this range, avalanches are found to reflect an intricate yet robust synchronization in which their mean size scales quadratically with duration, exhibiting an inverted parabolic profile with a scaling exponent of 2. These parabolic avalanches capture ongoing and evoked avalanches in the local field potentials (LFP) of nonhuman primates (Miller et al., 2019) and synchronized spiking from

awake transgenic mice using cellular resolution 2-photon imaging (Capek, Ribeiro et al., 2023; Srinivasan et al., 2024). However. the contribution of single neurons to the size of parabolic avalanches is currently not known.
Using cellular 2-photon imaging at high temporal and spatial resolution, we obtained and analyzed spiking activity in neurons expressing jRGECO1a in the contralateral anterior cingulate/medial prefrontal cortex of adult mice during quiet rest. Contrary to expectations for recurrent networks such as the cortex, we show that neurons contribute to a parabolic avalanche only once. This demonstrates that the growth of an avalanche is driven primarily by the recruitment of new neurons rather than by repeated spiking from previously active ones. To further investigate this, we developed a non-preferential recruitment model, where neurons are recruited without regard to their previous participation within an avalanche. This model closely replicated the behavior observed in properly resolved neuronal activity. Our results demonstrate that parabolic avalanches maximize their ability to include neurons in a synchronized cell assembly while democratizing the contribution of individual neurons. This finding supports cortical codes with neuronal identity over neuronal firing rates.

Disclosures: K. Srinivasan: None. **T.L. Ribeiro:** None. **D. Plenz:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.02/B123

Topic: B.07. Network Interactions

Support: NIH/ NINDS K08NS102526
2020 Doris Duke Charitable Foundation Clinical Scientist Career Development Award

Title: Phase amplitude coupling in vitro is developmentally regulated and specific to cellular composition

Authors: *C. W. HABELA[1], Y. SALIMPOUR[2], S. LIU[3], S. ODDOYE[1], W. S. ANDERSON[4], N. J. MARAGAKIS[5];
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Abstract: The extent to which human induced pluripotent stem cell (hiPSC)- derived neurons can recapitulate fundamental network behaviors required to process information in the brain is a major determinant of their utility in the study of normal development and disease. We recently demonstrated that networks of two-dimensional (2D) cultured hiPSC-derived cortical neurons grown with hiPSC-derived astrocytes on microelectrode array plates recapitulate the cross-frequency coupling (CFC) that is present *in vivo*. CFC and, more specifically, phase amplitude

coupling (PAC) is important in normal human cognition and altered in neurologic disorders including epilepsy and Parkinson's disease. Understanding the developmental time course and the cellular and molecular mechanisms of PAC *in vitro* has the potential to reveal therapeutic targets and more fully understand the underlying pathology of these disorders *in vivo*. We cultured hiPSC derived neurons and astrocytes and characterized their electrophysiologic and synaptic development over time. We employed the modulation index method for detecting phase-amplitude coupling (PAC) and correlated it with the maturation of GABAergic and glutamatergic synaptic activity. Further we analyzed changes in PAC in response to exogenous electrical and pharmacologic stimulation as well as cell specific optogenetic stimulation. We found that PAC is present, the degree of PAC is specific to network development, network structure, and cellular composition. It is modulated by external stimulation and manipulation of both GABAergic and glutamatergic signaling. These findings indicate that while PAC is reflective of network-level interactions, it is affected by specific cells in different ways and can be exogenously manipulated.

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Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.03/B124

Topic: B.07. Network Interactions

Support: NSF Research Initiation Award (HRD 1401026)
NSF IOS Neural Systems Awards (IOS 1755341 and 1755033)

Title: Role of Astrocytes in the Development of Neuronal Network Activity

Authors: *V. A. N. TALABATTULA[1], C. GROVER[2], M. MOORE[1], R. DZAKPASU[3], M. TEMBURNI[4];
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Abstract: Synchronous oscillations play a crucial role in establishing functional neural circuitry during vertebrate brain development. Current models of neuronal synchrony typically incorporate intrinsic neuronal properties, but astrocytes also contribute. At the tripartite synapse, they influence and modulate synaptic transmission by releasing gliotransmitters. As such, they have been shown to modulate network dynamics, but the mechanisms have not been widely studied. To assess the influence of astrocytes on neuronal network activity, we established neuron-only and mixed (astrocyte and neuron) cultures from the developing chicken optic tectum and forebrain. The purity of the neuronal cultures was confirmed by immunofluorescence imaging with anti-β;3 tubulin for neurons, and anti-GFAP or anti-vimentin for astrocytes. Single

cell recordings show no change in the membrane potential of neurons developing in the absence of astrocytes. However, on-cell recordings show striking differences in the firing patterns of constituent neurons in the neuron-only and mixed cultures. Lastly, we grew networks from both cultures on arrays of extracellular electrodes and recorded spontaneous network activity over several days. We assessed changes in spike and burst dynamics in a time-dependent manner and preliminary analyses demonstrated the importance of the physical presence of astrocytes in maintaining a viable neuronal circuit.
This study is supported by NSF Research Initiation Award (HRD 1401026) and NSF IOS Neural Systems Awards (IOS 1755341 and 1755033).

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Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.04/B125

Topic: B.07. Network Interactions

Support: 5R01AG066489-04
5TL1TR001451-09

Title: Circadian Differences in Locus Coeruleus Physiology

Authors: *R. RAE[1], L. L. MCMAHON[2];
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Abstract: The locus coeruleus (LC) is the primary producer of noradrenaline (NA) for the brain. This neurotransmitter plays a pivotal role in many behaviors including stress, anxiety, arousal, and as such, it strongly influences wake/sleep cycles. The LC is the primary source of the brain's noradrenaline (NA), and the activity of the LC-NA neurons is largely responsible for inducing wakefulness. Accordingly, LC-NA neurons show heightened activity during wakefulness, and alterations in their function in disease can impact sleep/wake cycles. Given its importance in behavior, a greater understanding of the precise activity of LC-NA neurons across the light-dark cycle is needed. This work investigates the single-unit electrophysiology of LC-NA neurons in middle-aged male Fischer rats recorded in vivo during the light phase (~ ZT4) and dark phase (~ZT 16) under isoflurane anesthesia (~1.8%). Single-channel tungsten electrodes were positioned into the LC, and in vivo electrophysiology recordings were acquired using an Omniplex recording system. LC activity was measured under basal conditions and in response to a mild footshock. The recorded activity was spike-sorted to identify unique units and signal processing was done in Matlab. The identity of LC-NA neurons was confirmed by inhibition of spiking activity ~30 mins after i.p. administration of the α2A antagonist, clonidine (0.1mg/kg).

LC burst activity was identified according to published criteria and defined as two or more consecutive spikes with an interspike interval (ISI) < 0.08 s, and terminated with an ISI > 0.16s. Based on the literature, our hypothesis was that even under anesthesia, units recorded from animals in the dark cycle would exhibit increased bursting activity as this is their time of wakefulness. Data was statistically analyzed with multilevel models with animal as the level 3 cluster(N=3), unit as the level 2 cluster (n=10) and burst as the level 1 event (n=~700). Count models (spike count, firing rate) were fitted utilizing a log linear model with a negative binomial distribution. We found that in response to footshock stimulation, dark animals exhibit an increase in burst firing rate ($p<.001$) and a higher number of spikes within a burst ($p<.001$). Interval outcomes were assessed using gaussian models and transformed appropriately to achieve normality of residuals. We found that units recorded from dark phase animals had decreased ISI within bursts ($p=.033$) and shortened interburst intervals ($p=0.013$). These findings support our hypothesis and suggest that the heightened activation of LC-NA neurons during wakefulness is influenced by a circadian mechanism independent of wake state.

Disclosures: R. Rae: None. **L.L. McMahon:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.05/B126

Topic: B.07. Network Interactions

Support: UK Research and Innovation (UKRI)
MSD (UK) Limited

Title: In vitro and in vivo investigation of network cortical hyperexcitability in the G93A-SOD1 mouse model of Amyotrophic Lateral Sclerosis

Authors: *M. DOULOUDI[1], J. WATKINS[2], J. DUCE[2], O. SHABIR[3], C. HOWARTH[3], J. BERWICK[3], M. LIVESEY[1], R. MEAD[1];
[1]Neurosci., Univ. of Sheffield, Sheffield, United Kingdom; [2]MSD R&D Innovation Ctr., London, United Kingdom; [3]Psychology, Univ. of Sheffield, Sheffield, United Kingdom

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a devastating disease characterized by the progressive degeneration of upper and lower motor neurons, with no effective treatment options available. Cortical hyperexcitability, an established early feature of ALS patients, is believed to contribute to locomotor circuit dysfunction and the subsequent injury and loss of motor neurons through excitotoxic cascades. Targeting cortical hyperexcitability holds great promise as a therapeutic strategy in ALS, but our understanding of the underlying mechanisms is incomplete, and the lack of suitable transgenic animal models impedes deeper investigation. In this extensive study, we utilized multi-electrode array (MEA) recordings coupled with cortical neurons derived from various ALS mouse models (G93A-SOD1, Q331K-TDP43 and FVB-C9ORF72 BAC) to

provide a detailed characterization of their longitudinal network properties and explore alterations in network excitability. Our findings revealed that among all the ALS models tested, only G93A-SOD1 cortical neurons displayed increased spontaneous network activity which was consistent with a hyperexcitable phenotype. Further mechanistic investigation uncovered dysfunction in inhibitory neurotransmission as a key factor driving network cortical hyperexcitability. To evaluate potential therapeutic interventions, we assessed the efficacy of several compounds/GABAergic potentiators in rescuing the hyperexcitable phenotype using this *in vitro* platform. Additionally, to assess early network cortical hyperexcitability *in vivo*, we employed multichannel microelectrodes in pre-symptomatic G93A-SOD1 mice and recorded stimulation-evoked neural data. Interestingly, preliminary data showed that the G93A-SOD1 mice showed heightened network synchronicity to whisker stimulation across the cortex compared to control mice, suggesting of cortical circuit dysfunctions. This study confirms the superiority of the G93A-SOD1 model in recapitulating early cortical dysfunctions both *in vitro* and *in vivo*, highlighting its utility for further preclinical drug discovery endeavors. The insights gained from this research can help in the better understanding of cortical hyperexcitability in ALS and provide a foundation for the development of targeted therapeutic strategies.

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Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

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Program #/Poster #: PSTR442.06/B127

Topic: B.07. Network Interactions

Support: DFG EXC 307
DFG SI 1332/3
ERC StG 335880
ERC CoG 864491

Title: Cell-class specific cortical-subcortical neuronal coupling in the primate brain

Authors: *J. LEE[1,2,3,4], C. V. NICOLAI[2,3,4], M. SIEGEL[2,3,4];
[2]Ctr. for Integrative Neurosci., [3]MEG Ctr., [1]Univ. of Tuebingen, Tuebingen, Germany; [4]Dept. Neural Dynamics and MEG, Hertie Inst. for Clin. Brain Res., Tuebingen, Germany

Abstract: Phase coupling of rhythmic neural activity is ubiquitous in the brain. It may not only reflect interactions in specific micro and macro circuits, but also play a role in regulating these interactions. Local and large-scale interactions involve a broad spectrum of distinct neuronal cell classes. However, little is known about how different cell classes are involved in phase-coupling across the brain. To address this, we investigated frequency-specific phase-coupling (pairwise-phase consistency) of different cell types across several cortical (frontoparietal) and subcortical

(thalamus and basal ganglia) brain regions in macaque monkeys that were performing a visual working memory task. We classified recorded single units into different cell classes based on extracellulary recorded spike waveforms. We found local (within region) and large-scale (across region) phase coupling of single units to the simultaneously recorded local field potential (LFP). This coupling was region-specific, frequency-specific, and dynamically modulated during the working memory task. Furthermore, phase coupling also differed between cell classes. Our findings provide insights into the variability of phase-locking dynamics across different cell types, highlighting their potential role in local and large-scale neuronal interactions.

Disclosures: J. Lee: None. **C.V. Nicolai:** None. **M. Siegel:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.07/B128

Topic: B.07. Network Interactions

Support: MathWorks Graduate Fellowship
RO1NS106031

Title: Cortical & thalamic population and spine dynamics during a visually-evoked 3-5 Hz rhythm

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

Abstract: 3-5 Hz oscillations are a prevalent feature of mouse cortex, driving spiking throughout sensory and motor areas. In V1, it's strongly evoked by sensory stimulation. Despite their prevalence and strength, we do not know the physiological function(s) of 3-5Hz activity. Proposed roles include memory replay, perception, plasticity or interareal synchronization. These hypotheses make predictions about the population dynamics of visually evoked 3-5Hz rhythms; if they're related to the perception or replay of preceding images, the oscillation should encode stimulus features, whereas a role in plasticity or synchronization implies that the rhythm should control spike cofiring or timing. To investigate these hypotheses, we presented images while recording either spiking using Neuropixels or single spine activity using iGluSnfr3 in mouse visual cortex. This allowed us to compare the short-latency response driven by images and persistent 3-5Hz oscillations from single-spine to network scales. First, we found that that 3-5Hz spiking drove an ensemble distinct from short-latency visually driven spiking, which occupied a separable population subspace. Surprisingly, image identity was not decodable from 3-5 Hz spiking. While the evoked response scaled in dimensionality with the number of stimuli presented, 3-5Hz dimensionality remained constant across image sets. Though independent from preceding stimuli, 3-5Hz had precise structure in its laminar organization and spike timing. 3-5Hz activity was comprised of brief up-states dominated by L5 pyramidal cells which fired first

and most consistently. Conversely, L2/3 fired with greater latencies and less consistency. During these up-states, cells cofired with tight temporal precision, consistent with a role in synchronization or plasticity. To determine if similar dynamics were present in thalamus, we recorded from dLGN and found a 3-5Hz rhythm synchronous with cortex. Just as in cortex, the rhythm recruited a thalamic population in a separable subspace from the evoked response unrelated to the inducing image. Finally, we used iGluSnFr3 to image the synapses associated with the rhythm in V1. Image presentation evoked a robust 3-5 Hz oscillation visible in single-trial glutamate dynamics. The oscillation recruited a separable yet overlapping ensemble of spines to the short-latency evoked response (similar to spiking). Together, our results show that 3-5Hz dynamics engage different groups of cells and synapses from stimulus driven activity, suggesting it doesn't organize perception or replay. However, the co-firing mediated by this rhythm is suggestive of a role in neural plasticity or synchronization.

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

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.08/B129

Topic: B.07. Network Interactions

Support: CIHR Grant 426485

Title: Investigating claustrum processing of anterior cingulate inputs

Authors: *T. SHAKER, M. ALMOKDAD, J. C. JACKSON;
Univ. of Alberta, Edmonton, AB, Canada

Abstract: The anterior cingulate cortex (ACC) is a high-order cortical region that regulates cognitive functions, such as attention. Anatomical data show that the ACC strongly innervates the claustrum (CLA), a small nucleus in the forebrain, suggesting that ACC inputs can participate in modulating CLA activity. To date, functional characterization of the physiological mechanisms underlying ACC-CLA networks has been mainly studied in brain slices derived from rodents. However, such mechanisms are yet to be explored *in vivo*. Therefore, we performed *in vivo* extracellular recording of CLA neurons in head-fixed C57BL/6 mice while optogenetically stimulating excitatory ACC projection neurons. To achieve this, we introduced silicon probes into the CLA in order to record the response of CLA neurons to ACC photo-stimulation. After each recording, post hoc histological analysis was used to confirm probe placement in the CLA. Local field potentials revealed that ACC stimulation elicited a biphasic response in the CLA composed of an early excitatory component with a small amplitude, followed by a late inhibitory component with a significantly larger amplitude. These results suggest that ACC projections modulate both excitatory and inhibitory CLA neurons. Further,

recording single-unit activity in the CLA demonstrates that 55% of putative excitatory neurons were inhibited following ACC stimulation, whereas 27% were activated, and 18% showed no response. On the other hand, 52% of putative inhibitory neurons were activated following ACC stimulation, whereas 24% were inhibited, and 24% showed no response. Our findings indicate that ACC input facilitates robust suppression of excitatory activity within the CLA. Future studies will explore the identity of CLA inhibitory neurons predominantly targeted by ACC projections that mediate overall inhibition of CLA output.

Disclosures: T. Shaker: None. **M. Almokdad:** None. **J.C. Jackson:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.09/B130

Topic: B.07. Network Interactions

Support: NIH F32 NS116416
NIH R01 NS136590-01
CURE Taking Flight Award
Friedman Brain Institute Postdoctoral Innovator Award

Title: Parvalbumin-expressing inhibitory theta phase locking in the healthy and epileptic hippocampus impacts seizure susceptibility

Authors: *Z. CHRISTENSON WICK[1], P. A. PHILIPSBERG[1], C. KOHLER[2], S. I. LAMSIFER[3], E. KATANOV[4], Y. FENG[5], L. M. VETERE[1], D. J. CAI[6], T. SHUMAN[1]; [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Mount Sinai Sch. of Med., New York, NY; [3]Nash Family Dept. of Neurosci., Mount Sinai Sch. of Med., New York, NY; [4]Neurosciences, Mount Sinai, Queens Village, NY; [5]Neurosci., Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [6]Mount Sinai, New York, NY

Abstract: Network-wide oscillations, such as theta, orchestrate and organize the spiking of individual neurons in a phenomenon known as phase locking, which has long been thought to maintain excitatory-inhibitory homeostasis and coordinate cognitive processes. Using the pilocarpine mouse model of temporal lobe epilepsy, we've found altered theta phase locking of inhibitory neurons in the dentate gyrus of epileptic mice with spontaneous seizures and cognitive deficits. While phase locking has been widely studied in a variety of contexts using correlational methods, the direct, causal influence of this phenomenon has never been determined. Thus, we aimed to directly test the hypothesis that inhibitory theta phase locking can bidirectionally control seizure susceptibility in control and epileptic mice. To test this hypothesis, we developed a low-latency closed-loop optogenetic system (PhaSER) to bidirectionally control inhibitory phase locking to theta in head-fixed control and pilocarpine-treated epileptic mice navigating a virtual track. Using opto-tagging strategies, we first identified the preferred firing phase of

parvalbumin (PV)+ and somatostatin (SOM)+ dentate interneurons in control and epileptic mice. We then applied our closed-loop system to lock the spiking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring latency to seize after a systemic kainic acid injection. Using opto-tagging strategies, we found a cell-type specific deficit in theta phase-locking of PV, but not SOM neurons in the dentate gyrus of chronically epileptic mice. Furthermore, we have found that mis-aligning inhibitory spiking to the peak of theta increases seizure susceptibility in otherwise healthy, control mice and that re-aligning inhibitory spiking to the trough of theta diminishes seizure susceptibility in epileptic mice. Together, these data suggest that theta phase locking of inhibitory spiking plays an important and causal role in seizure susceptibility. Gaining deeper insights into the impacts of inhibitory theta phase locking may reveal the potential of oscillation-driven stimulation as an effective epilepsy therapeutic, and the direct influence that inhibitory theta phase-locking holds over network-wide activity.

Disclosures: Z. Christenson Wick: None. **P.A. Philipsberg:** None. **C. Kohler:** None. **S.I. Lamsifer:** None. **E. Katanov:** None. **Y. Feng:** None. **L.M. Vetere:** None. **D.J. Cai:** None. **T. Shuman:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.10/B131

Topic: B.07. Network Interactions

Support: NIH T32GM007739
HDRF 203840-01

Title: Effect of intermittent theta burst stimulation on synchrony in the medial prefrontal cortex

Authors: *R. MIKOFSKY[1], S. B. JOHNSON[3], H. ASHER[3], C. M. LISTON[2];
[1]Neurosci. / Psychiatry, [2]Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY;
[3]Weill Cornell Med., New York, NY

Abstract: Depression is a primary cause of disability globally, with a significant proportion of patients failing to respond to traditional interventions. Accelerated intermittent theta-burst stimulation (iTBS) of dorsolateral prefrontal cortex (dlPFC) is a recently developed form of transcranial magnetic stimulation (TMS) that shows rapid, robust remission rates in some patients with treatment-resistant depression. However, further optimization of this therapy is limited by poor understanding of the cellular and circuit mechanisms of iTBS. To explore these mechanisms, we developed an optogenetic model of iTBS in mice, using the left prelimbic cortex (lPL) as a correlate of the dlPFC. iTBS sessions consisted of 50 Hz triplet pulses (5ms duration, 2mW, 465nm LED) repeated every 200 ms for 2 sec with an 8 sec off period over a 10 min session (1,800 pulses total) followed by a 50 min inter-session interval. Recent advances in cutting-edge ultra-high-density in vivo extracellular electrophysiology probes have allowed for

recording of neural activity from 1024 electrodes simultaneously at 20kHz sample collection rate, enabling single-cell resolution activity, across superficial and deep brain circuits, over multiple regions (6 mm² area). Here we use this technology to perform repeated acute recordings in PFC (bilateral, shallow and deep layers) before, during and after optogenetic iTBS stimulation over a 5-day period. We find that repeated sessions of iTBS across days drives increased synchrony across the PFC that persists after stimulation. These findings suggest a possible mechanism of increased functional connectivity that may underlie behavioral effects of accelerated iTBS TMS therapy. In ongoing work, we are using optogenetic-tagging with this recording method to determine critical cell types involved in these persistent, circuit-level changes.

Disclosures: R. Mikofsky: None. **S.B. Johnson:** None. **H. Asher:** None. **C.M. Liston:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.11/Web Only

Topic: B.07. Network Interactions

Support: SEPI-IPN Grant No 20171402
SEPI-IPN Grant No 20242113
INPRF NC 123240.1

Title: Gaba b receptors in the external globus pallidus modulate cortex beta oscillation through control thalamic reticular nucleus activity

Authors: *N. VILLALOBOS VÁSQUEZ[1], V. M. MAGDALENO-MADRIGAL[2];
[1]Academia de Fisiología-Sección de Estudios de Posgrado e Investigación, Inst. Politécnico Nacional- Escuela Supereior de Medicina, Ciudad de México, Mexico; [2]Dirección de Investigación en Neurociencias, Inst. Nacional De Psiquiatría Ramón de la Fuente Muñiz, Ciudad De México, Mexico

Abstract: The external globus pallidus (GP) synchronizes the basal ganglia-thalamus-cortex circuit by GABAergic output to different nuclei. Thus, a pair of evidence is significant. First, the firing rate and the GABAergic transmission to output nuclei of GP are modulated by GABA B receptors. Second, the pathway presence between the GP and thalamic reticular nucleus (RTn). The physiological contribution of GABA B receptors of GP through this network in cortical dynamics is feasible because the RTn modulates information flow between the thalamus and cortex. To assess this hypothesis, we recorded at the same time the extracellular single-unit activity of RTn neurons and electroencephalogram of the motor cortex (MCx) before and after GP injection of the GABA B agonist baclofen and the antagonist saclofen in anesthetized rats. We found that the firing rate of the RTn increases after GABA B agonism, and this response decreases the spectral density of beta frequency bands in the MCx. Further, antagonism of

GABA B receptors lessens the firing activity of the RTn and reverses the effect in the power spectra of beta frequency bands in the MCx. Our results give evidence that the GP modulates cortical oscillation dynamics through the GP-RTn network via modulation of RTn activity by GABA B receptors.

Disclosures: N. Villalobos Vásquez: None. **V.M. Magdaleno-Madrigal:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.12/B132

Topic: B.07. Network Interactions

Support: NIH Grant 5R01NS123396

Title: Contribution of projection neuron subtypes to gamma oscillations in the rat primary motor cortex

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

Abstract: Oscillatory activity occurring within the primary motor cortex (M1) at frequencies in the gamma band (30-80 Hz) is associated with skilled motor movements. While this phenomenon is well documented across animal and human subjects, its recruitment of projection neuron subtypes has received little attention. Our research addresses this question by investigating the propensity of four projection neuron (PN) subtypes to entrain and promote gamma in M1: Layer 2/3 intratelencephalic neurons, Layer 5 pyramidal tract (PT) and cross-corticostriatal (CCS), and Layer 6 corticothalamic (CT). A growing literature has been exploring the contributions of PT neurons and intratelencephalic (IT) neurons, of which CCS neurons are a subclass, to controlling complex motor behavior. A few studies suggest that the activity of PT cells are more strongly linked to gamma than IT cells. Neuroanatomical literature also suggests that the connectivity of PT cells is more suitable for supporting fast oscillations than the other subtypes. We thus hypothesized that PT cells will show the strongest tendency to entrain to and support gamma. To test this, we adopted a two-pronged approach. First, we examined their proclivity to induce gamma with optogenetic and patch clamp methods in ex vivo slice preparations. Specifically, we optogenetically excited specific PN subtypes somatically expressing ChroME with a ramping blue light stimulus while obtaining whole-cell patch recordings from adjacent, non-opsin positive, neurons to observe gamma oscillations elicited in the local network. Second, we examined the anatomical connectivity between PN subtypes and parvalbumin positive (PV) interneurons, who are crucial players in the generation and maintenance of gamma oscillations. To do this, in PV-cre transgenic rats we labeled the presynaptic terminals of PV interneurons with AAV1-Flex-tdTomato-SypEGFP and the somata

of PNs in a projection-specific manner using the retrograde tracers fast blue and CTB-Alexa647. This allowed us to visualize and quantify the synaptic inputs each subtype receives from PV cells. We found that optogenetically activating PNs induces in vivo-like gamma oscillations across layers 2/3, 5, and 6 in M1. Each PN subtype appears capable of eliciting gamma oscillations in the slice. Thus far, there is a tendency for the rhythms to be strongest when driven by PT neurons, and weakest for CT. Our anatomical experiments also reveal a trend of PT neurons receiving more synapses from PV+ cells than other subtypes. This work provides experimental support for PN subtype-specific contributions to gamma in cortical microcircuits.

Disclosures: D. Kim: None. **D. Headley:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.13/B133

Topic: B.07. Network Interactions

Support: MC_UU_00003/6
Wellcome Trust Senior Research Fellowship 224430/Z/21/Z

Title: Enhancing motor cortical theta and gamma oscillations using closed-loop phase-dependent optogenetic stimulation

Authors: *J. L. MYATT[1], R. TOTH[2], C. G. MCNAMARA[3], C. STAGG[2], A. SHAROTT[4]; [1]Nuffield Dept. of Clin. Neurosciences, [2]Brain Network Dynamics Unit, Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom; [3]Univ. Col. Cork, Cork, Ireland; [4]Nuffield Dept. of Clin. Neurosciences, Brain Network Dynamics Unit, Oxford, United Kingdom

Abstract: Neuronal oscillations are a prominent feature of motor cortical local field potentials (LFPs) and abnormalities in oscillatory activity have been linked to several disorders. Theta-modulated gamma-frequency pulses of alternating current stimulation are known to modulate motor learning in humans, however, it is unclear how these frequencies modulate motor cortical activity at the cellular microcircuit level. Here, we aimed to develop a method for bidirectionally modulating theta and gamma coupled oscillations in the motor cortex using closed-loop optogenetic stimulation of excitatory RBP4-Cre (retinol-binding-protein-4) or PV-Cre (parvalbumin) inhibitory interneurons. Motor cortical LFPs were recorded in mice in which these neurons were transfected with Channelrhodopsin-2. Using our recently developed phase-tracking system (Oscilltrack), blue-light pulses were delivered at four phases of the ongoing motor cortical theta oscillation in awake, head-fixed mice. Optogenetic stimulation was delivered over a quarter of the theta cycle, either as a continuous pulse or a burst of three pulses at gamma frequency (75Hz). Both stimulation types modulated theta power in a phase-dependent manner, with continuous stimulation of excitatory cells leading to stronger modulation. Phase-dependent amplification during stimulation of excitatory vs inhibitory neurons was offset by 90°, in line

with predictions from computational models of excitatory/inhibitory circuits. These same phase-specific effects did not occur when previously recorded closed-loop stimulation patterns were replayed to the mice, demonstrating that these effects were not due to stimulation pattern. While gamma oscillations were broadly modulated by all stimulation types for excitatory neurons, the strongest effect was induced by gamma stimulation, leading to a clear 75Hz peak. These results were not dependent on the phase of theta oscillation targeted. These findings demonstrate that phase-dependent modulation of theta power can be mediated by stimulation of excitatory or inhibitory neurons, and that the effect of specific stimulation phases is likely to be the result of interactions between these populations. Moreover, theta phase-dependent optogenetic stimulation of excitatory, but not inhibitory, neurons could be a more effective method of driving cortical gamma power. This approach can be used to inform the development of brain stimulation methods to modulate these activities in humans.

Disclosures: J.L. Myatt: None. **R. Toth:** None. **C.G. McNamara:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Oxford. **C. Stagg:** None. **A. Sharott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Oxford.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.14/B134

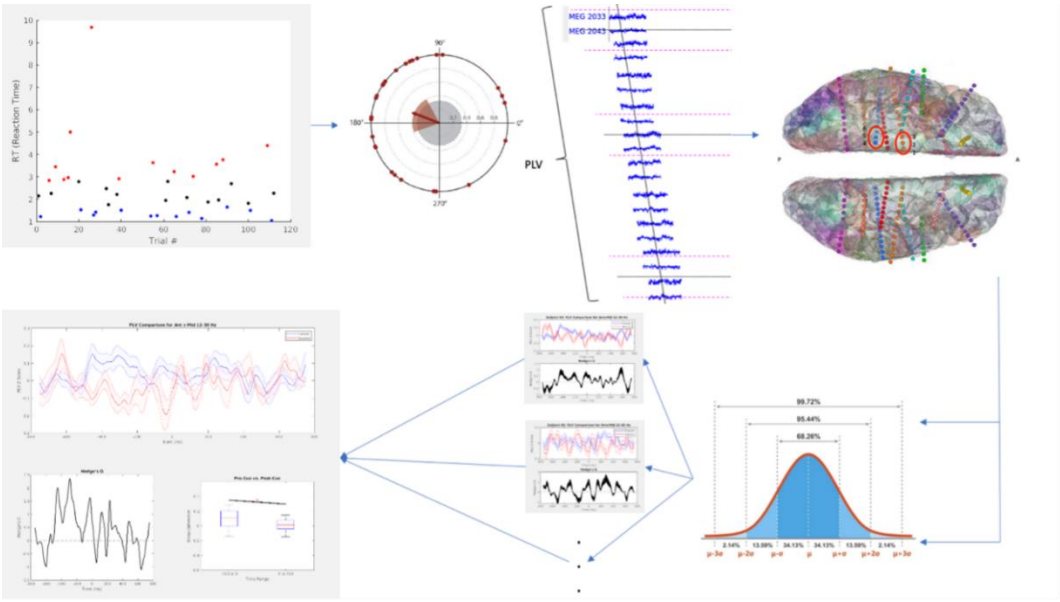
Topic: H.04. Executive Functions

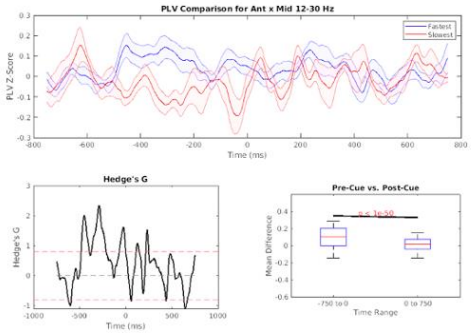
Title: Intra-thalamic Neurophysiologic Synchrony In the Context of Mathematical Cognition

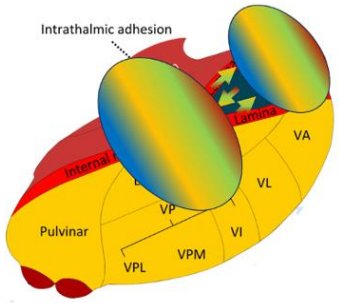
Authors: *B. SHERMAN[1,2], B. REID[3], M. HEDLUND[4], J. PARVIZI[5], V. BUCH[6];
[1]Drexel Univ. Col. of Med., Philadelphia, PA; [2]Neurosurgery, Stanford University School of Medicine, Stanford, CA; [3]Stereotactic and Functional Neurosurg., Stanford Univ., Palo Alto, CA; [4]Stanford Univ., Stanford, CA; [5]Stanford Univ. Sch. of Med., Stanford, CA; [6]Neurosurg., Stanford Univ., Palo Alto, CA

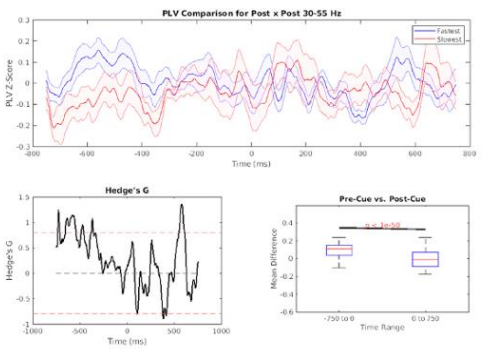
Abstract: Cognitive control is exercised in mathematical cognition. The role of intra-thalamic interactions in mathematical cognition remains unexplored in humans. We aim to investigate the dynamic interactions between thalamic anatomic nodes during mathematical cognition. Stereotactic EEG data was recorded from patients undergoing monitoring for refractory epilepsy. While in the EMU patients completed tasks involving mathematical reasoning, and neural data were processed by computing phase locking value (PLV) between anatomically partitioned contacts from anterior, mid and posterior thalamus(Figure 1). These were compared for fast and slow responses within and across subjects.
Across subjects anterior-mid thalamic connectivity in the preparatory period demonstrated significantly increased beta band PLV preceding fast trials (12-30 Hz), and intra-Pulvinar

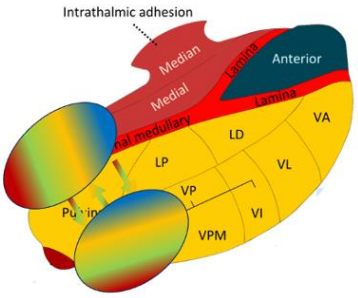
connectivity in the low gamma band (30-55 Hz) immediately after the prior trial preceding enhanced performance in the upcoming trial (Figure 2). Pre-cue and post-cue differences were significant for both ($p < 1e-50$). These patterns were consistent within subjects.
Our findings reveal significant dynamic interactions within the thalamus. These first in human findings advance our understanding of the thalamic mechanisms in cognitive control and offer a foundational perspective for future therapeutics targeting network pathologies in LID.











Disclosures: B. Sherman: None. **B. Reid:** None. **M. Hedlund:** None. **J. Parvizi:** None. **V. Buch:** None.

Poster

PSTR442: Circuit Mechanisms of Oscillations and Synchrony

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR442.15/B135

Topic: B.07. Network Interactions

Support: NINDS Translational Neuroscience T32 5T32NS115723-04

Title: Propofol induced burst suppression evokes neuronal firing and local field potential traveling waves in the human brain

Authors: *V. ZARR[1], P. A. HOUSE[2], B. GREGER[3], T. DAVIS[1], E. H. SMITH[4];
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Abstract: Despite substantial work, the spatiotemporal neural dynamics underlying medically induced loss of consciousness (mLOC) remain a mystery. Neural traveling waves are electrical perturbations that propagate across the brain with systematic phase delays. Recent work has characterized traveling wave propagation mechanisms in non-human primates (NHP) during mLOC and showed that they change directions. Prior work has shown the presence of burst suppression firing during mLOC. However, ours is the first study to characterize the spatiotemporal dynamics of traveling waves in human action potential and local field potential (LFP) activity during mLOC. We hypothesized that burst suppression evokes brain oscillations that propagate as traveling waves. We examined direct brain recordings during propofol induced loss of consciousness, from Utah-style microelectrode arrays from two adult patients with intractable epilepsy who were undergoing monitoring for surgical treatment for medically resistant seizures. Upon identification of burst suppression, we then regressed the timing of LFP and neuronal firing against the two spatial dimensions of the microelectrode array. We operationally defined traveling waves as regression models with slopes that significantly differed from zero, assessed via an F-test against a permutation distribution of 500 spatially shuffled LFP or firing times. We fit these models with both L1 and L2 regularization for both types of signals, and controlled for false positives with permutation testing. We recorded a total of 96 LFPs and 71 single unit recordings for patient one. Out of 93 total bursts in patient one, traveling waves were identified from 28% of LFPs and from 46% of single unit recordings, using the L1 regularization regression model, respectively. Using the L2 regularization regression model, traveling waves were identified from 42% of LFPs and from 27% of single unit recordings, respectively. We recorded a total of 52 LFPs and 70 single units for patient two. Of the channels recorded, traveling waves were identified from 17% of LFPs and from 26% of single unit recordings, using the L1 regularization regression model, respectively. Using the L2

regularization regression model, traveling waves were identified from 24% of LFPs and from 23% of single unit recordings. We therefore showed that neural activity during burst suppression propagated as traveling waves, suggesting that subsequent research into anesthesia burst suppression evoked traveling waves may identify spatiotemporal signatures of traveling waves that can differentiate among consciousness states.

Disclosures: V. Zarr: None. **P.A. House:** None. **B. Greger:** None. **T. Davis:** None. **E.H. Smith:** None.

Poster

PSTR443: Network Dynamics and Interactions

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: /

Topic: B.07. Network Interactions

Title: Impaired Somatosensory Integration Resulting from Motor Cortex Cavities

Authors: *U. KILIC[1,2], Z. DENG[3], M. MC LAUGHLIN[4], B. NUTTIN[3];
[1]Catholic Univ. of Leuven, Leuven, Belgium; [2]Department of Neurosciences, KU Leuven, Leuven, Belgium; [3]KU Leuven, Leuven, Belgium; [4]Neurosci., KU Leuven, Leuven, Belgium

Abstract: Sensory integration is crucial in motor control, particularly in the context of stroke rehabilitation. Recent studies show that inhibition of the somatosensory cortex (S1) results in motor disturbances [1]. Conversely, damage to the motor cortex (M1) causes dynamic changes in the somatosensory cortex [3]. This highlights how reciprocal connections between M1 and S1 are affected by injury, emphasizing the importance of understanding their interaction for rehabilitation. To achieve this goal, we investigated altered evoked potentials (EP) in M1 and S1 after induction of an abnormal brain cavity (ABC) in the motor cortex. In this study, we use male Sprague-Dawley rats weighing between 275 and 350 grams. As a model of the ABC, we aspirated the motor cortex. Subsequently, employing a 32-channel silicon probe, we recorded EPs in the primary motor cortex (M1) elicited by neuromuscular electrical stimulation (NMES) across three conditions: healthy rats, rats with acute cavity formation (within hours of induction), and rats with chronic cavity formation (1-week post-induction). Additionally, in a separate cohort of rats (n = 8), we simultaneously recorded evoked potentials from both the primary motor cortex (M1) and the primary somatosensory cortex (S1). After inducing an ABC solely in M1, we replicated these measurements, maintaining the simultaneous recording setup. **Data collection is still ongoing**. Our analysis will focus on assessing the latency and amplitude of the initial negative deflection. A linear mixed-effects model will be employed for statistical analysis. Preliminary results indicate distinct responses to NMES in S1 and M1, characterized by differences in latency and amplitude. Specifically, S1 exhibits earlier responses (mean latency = 20.4 ± 9.28 milliseconds), while M1 responses are delayed (mean latency = 52.4 ± 14.58 milliseconds). Moreover, there's a variance in amplitude, with S1 responses displaying higher mean amplitudes (mean = 399 ± 277 microvolts) compared to M1 (mean = 182 ± 99 microvolts).

Post-induction of ABC, we observed a reduction in EP amplitude in the ABC-affected wall, whereas amplitude is preserved in S1. Further analysis will elucidate additional intricate changes in the cortices, which holds promise for providing tools for post-stroke recovery. **References** 1. Friel, K.M., et al., *Dissociation of sensorimotor deficits after rostral versus caudal lesions in the primary motor cortex hand representation.* J Neurophysiol, 2005. **94**(2): p. 1312-24. 2. Fukui, A., et al., *Layer-specific sensory processing impairment in the primary somatosensory cortex after motor cortex infarction.* Scientific Reports, 2020. **10**(1): p. 3771.

Disclosures: U. Kilic: None. **Z. Deng:** None. **M. Mc Laughlin:** None. **B. Nuttin:** None.

Poster

PSTR443: Network Dynamics and Interactions

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Program #/Poster #: PSTR443.01/B136

Topic: B.07. Network Interactions

Support: JSPS KAKENHI JP24K18267
JSPS KAKENHI JP21K15247
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JSPS KAKENHI JP23K18485
JSPS KAKENHI JP23H03488
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JSPS KAKENHI JP22H05698
JSPS KAKENHI JP21H03606
JSPS KAKENHI JP23K21755
JSPS KAKENHI JP21K06702
JSPS KAKENHI JP20H04341

Title: Voltage-sensitive dye imaging functional dissection of ipsilateral and contralateral neural activity propagation in mouse anterior cingulate cortex (ACC)

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Abstract: The prefrontal cortex (PFC) is essential for integrating higher brain activity, and disruption can lead to schizophrenic and other neuropsychiatric phenotypes. The intrahemispheric activity and interhemispheric connection significantly influence the pathology of neuropsychiatric disorders. The aim of this study was to generate a functional map of the intra- and inter-hemispheric connections of the PFC. Functional dissection of the mouse PFC, particularly at the anterior cingulate cortex (ACC), was performed using the voltage-sensitive

dye (VSD) imaging method with high speed (1 ms/frame), high resolution (256 × 256 pixels; MiCAM05, Brainvision, LTD., Japan), and a large field of view (approximately 10 mm). Acute serial 350 µm slices were prepared from the bregma covering the PFC and numbered 1-5 based on their distance from the bregma (i.e., 1.70, 1.34, 0.98, 0.62, and 0.26 mm) with reference to the Mouse Brain Atlas (Paxinos and Franklin, 2008). Imaging analysis revealed directional biases in neural signals traveling within the ACC, with the speed and probability of signal transmission varying with signal direction. Specifically, neural signal propagation from cg2 to cg1 was stronger than from cg1 to cg2, with implications for interhemispheric functional connectivity. The neural response to electrical stimulation was measured at nine sites and then averaged to create a functional map of the propagation patterns. Intracortical propagation was observed in slices 3-5: slices containing the anterior cingulate cortex (ACC) and the corpus callosum (CC). Activity reached area 33 of the ACC. Faster acquisition (300 µs/frame) focused on cg2 showed that the activity spread from layers II/III to the deeper layer and reached the border of the CC. The activity in CC did not appear in VSD imaging, but the subsequent activation first appeared in the same area in the contralateral hemisphere. Direct white matter stimulation activated cg2 in both hemispheres. Similar results were obtained with Di-I staining of the CC. This finding could pave the way for more effective treatments for neuropsychiatric disorders. The functional map created with VSDI is a powerful tool for exploring functional connections in the brain and could provide valuable insights into how the brain processes information.

Disclosures: Y. Tominaga: None. **M. Taketoshi:** None. **T. Tominaga:** None.

Poster

PSTR443: Network Dynamics and Interactions

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Topic: B.07. Network Interactions

Support: R01MH113007 from NIMH

Title: Spontaneous firing characteristics of BNST neurons in brain slices: role of $GABA_A$ tonic inhibition

Authors: *W. FRANCESCONI[1], F. BERTON[2], S. LOSEE OLSON[3], J. A. DABROWSKA[4]; [1]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL; [2]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ., North Chicago, IL; [3]Rosalind Franklin Univ., NORTH CHICAGO, IL; [4]Chicago Med. Sch. RFUMS, North Chicago, IL

Abstract: The dorsolateral bed nucleus of the stria terminalis ($BNST_{DL}$) neurons are mainly GABAergic, and the $BNST_{DL}$ output is regulated by local GABAergic activity. Based on their intrinsic membrane conductance, $BNST_{DL}$ neurons are classified as Type I, II and III. Although $BNST_{DL}$ neurons receive synaptic inhibitory and excitatory inputs from local neurons, they don't show spontaneous firing *in vitro*, while *in vivo* $BNST_{DL}$ neurons have spontaneous firing around

4 Hz. Whereas spontaneous firing is rarely observed in brain slices *in vitro* in "traditional" aCSF, neurons from slices in aCSF with an ionic composition like to the brain interstitial fluid, exhibit a spontaneous firing similar to the *in vivo* recordings. The temporal features of spontaneous firing, critical for neuronal communication, are strongly regulated by extrasynaptic $GABA_A$ receptors. Using aCSF containing in mM: 1 Ca^{2+}, 0.5 Mg^{2+} and 4.5 K^+, we recorded in current clamp mode the spontaneous firing in all three types of $BNST_{DL}$ neurons. The temporal features of spontaneous firing include the measure of Coefficient of variation (CV), Fano factor (Fano) and spontaneous firing rate (FR). The CV and Fano less than 1 indicate regular firing neuron, while CV and Fano higher than 1 characterize a bursting neuron. The statistical analysis revealed significant differences between Type I-II neurons grouped and Type III neurons for each parameter. The CV was 0.523 ± 0.14 in Type I-II and 1.86 ± 0.57 in Type III (*P*=0.0019, unpaired t-test). The Fano was 0.415 ± 0.31 in Type I-II and 3.412 ± 1.09 in Type III (*P*=0.0085). The FR was 2.59 ± 0.5 Hz in Type I-II and 1.0 ± 0.09 Hz in Type III (*P*=0.0547). We then studied the effects of $GABA_A$ blocker PTX (100 μM) on the spontaneous firing characteristics in Type I-II and Type III neurons. The statistical analysis revealed no significant effect of PTX on CV, Fano and FR in Type I-II neurons (CV: pre 0.523 ± 1.14; PTX 0.54 ± 0.18; post 0.7 ± 0.31(F(0.2054, 1.027)=0.05978, *P*=0.4383, n=8); Fano: pre 0.414 ± 0.31; PTX 0.522 ± 0.43; post 0.619 ± 0.45 (F(0.6819, 3.068)=0.5201, *P*=0.4522, n=7); FR (Hz): pre 2.592 ± 0.5; PTX 2.603 ± 0.36; post 2.455 ± 0.74 (F(0.2183, 1.092)=0.1457, *P*=0.3951, n=8)). However, in Type III neuron PTX reduced CV: 1.86 ± 0.37 (pre); 0.86 ± 0.08 (PTX); post 1.3 ± 0.38 (F(1.254, 3.762)=5.491, *P*=0.0813, n=4); Fano: 3.41 ± 1.09 (pre); 0.525 ± 0.07 (PTX); 2.2 ± 0.85 (post) (F(1.432, 4.296)=6.319, *P*=0.0596, n=4); FR (Hz) increased from 1.00 ± 0.09 (pre) to 1.342 ± 0.13 (PTX); post 1.0 ± 0.17 (F (1.332, 3.997)=5.313, *P*=0.0796, n=4). In conclusion, blockade
of $GABA_A$ inhibition does not influence Type I-II neurons regular firing but it changes the firing of Type III $BNST_{DL}$ neurons from bursting to regular.

Disclosures: W. Francesconi: None. **F. Berton:** None. **S. Losee olson:** None. **J.A. Dabrowska:** None.

Poster

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Topic: B.07. Network Interactions

Support: TLL Core funding
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Title: Noise filtering via local inhibitory circuits of the claustrum

Authors: M. GRAF[1], S. SADEH[2], *G. J. AUGUSTINE[1];
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Abstract: We used optogenetic circuit mapping to characterize the function and spatial organization of inhibitory circuits formed by interneurons (INs) within the claustrum, a poorly understood brain region. The properties of these circuits were incorporated into a computational model that predicted distinct roles for each interneuron type in determining claustrum output. Interneurons expressing parvalbumin (PV) or somatostatin (SST) inhibit projection neurons and thereby attenuate claustrum output, while interneurons expressing vasoactive intestinal peptide (VIP) promote claustrum output via disinhibition of projection neurons. Differential inhibition of cortical or subcortical projection neurons leads to toggling of claustrum output between these two brain regions. Further, due to the convergence of multiple INs onto their postsynaptic targets, inputs are spatially filtered by local INs to yield non-linear inhibition that depends on the amplitude and spatial distribution of excitatory input to the claustrum. Such non-linear filtering is maximal for neurons receiving weak excitation, and minimal for neurons with strong excitatory input. The widespread connectivity of claustral INs causes them to integrate spatial input differences across the claustrum, resulting in minimal inhibition at the center and maximal inhibition at the periphery. The spatial filtering effects are the largest for broadly-connected SSTs and the smallest for sparsely-connected VIPs. These local signal processing mechanisms allow the claustrum to act as a high-pass filter that transmits larger input signals, while suppressing weaker, noise-like signals. These findings suggest that the function of the claustrum is to provide a de-noised feedback signal that improves the fidelity of signal processing in downstream areas.

Disclosures: M. Graf: None. **S. Sadeh:** None. **G.J. Augustine:** None.

Poster

PSTR443: Network Dynamics and Interactions

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Topic: B.07. Network Interactions

Support: NIH DIRP ZIAMH002797

Title: Recovery of avalanche dynamics in frontal cortex following acute ketamine administration in a mouse model for depression

Authors: *P. KELLS, Y. BIBINEYSHVILI, V. SINFUEGO, T. L. RIBEIRO, D. PLENZ; Sect Critical Brain Dynamics, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: In 2019, ketamine (KET) received breakthrough therapy status for treatment resistant depression (TRD). Yet, the neural mechanisms by which a single, sub-anesthetic dose of KET alleviates depression for up to 1 week are not well understood. Using the corticosterone animal model for depression, here, we assess the effects of KET in depressed mice on cortical network dynamics. We stably expressed the red-shifted GECI jRGECO1a in the anterior cingulate/medial prefrontal cortex of adult male mice (N=17; >P35; C57BL/6). A dorsal, chronically implanted

cranial window combined with a micro-prism allowed us to image across the midline in the intact contralateral cortex. We simultaneously recorded ~200 neurons in layer 2/3 during quiet rest using cellular-resolution 2-photon imaging (2PI) to obtain corresponding spiking probabilities at high temporal resolution (22 ms). Mice received in their home cage ad libitum water containing either corticosterone at 0.1mg/mL+1% ethanol (DEP) or normal drinking water (CTRL). After 3 weeks, the corticosterone-induced depression phenotype was established by showing an increase in relative anhedonia to baseline in the sucrose preference test (DEP: 1.61±0.74, CTRL: 0.82±0.41, $p<0.001$). The effect of a single injection of 10mg/kg sub-anesthetic dose of KET in depressed (DEP-KET) or control animals (CTRL-KET) was compared in addition to depressed animals that received a single saline injection (DEP-SAL) to control for spontaneous recovery from depression. 30-min recordings of quiet rest were conducted every 2-3 days to establish baselines and DEP/CTRL-treatment conditions followed by 1hr, 1d, 3d, and 7d timepoints post-injection (KET/SAL). Number of cells imaged (~200), mean spike rates (~1 spike/s), and mean pairwise correlations (~0.025±0.01) were stable across the experimental timeline (5-weeks) within groups and did not differ significantly between groups. In contrast, higher-order cortical dynamics in the form of neuronal avalanches were significantly altered in the depressed state and in response to treatment. CTRL animals displayed scaling in mean avalanche size with avalanche duration close to 2, whereas scaling was significantly reduced in DEP animals. Preliminary results suggest that avalanche scaling was rescued at 3- and 7-days after the KET injection in DEP animals. KET did not change scaling in CTRL animals. Our results demonstrate that avalanche dynamics are significantly altered in the frontal cortex of depressed mice, and recover after a single sub-anesthetic dose of ketamine. We suggest that ketamine improves treatment-resistant depression by re-establishing a critical state in frontal cortex.

Disclosures: P. Kells: None. **Y. Bibineyshvili:** None. **V. Sinfuego:** None. **T.L. Ribeiro:** None. **D. Plenz:** None.

Poster

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Topic: B.07. Network Interactions

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Title: Effect of BDNF on subicular circuits in vitro

Authors: *G. MACCAFERRI[1,2];
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Abstract: The downregulation of the KCC2 transporter in subicular neurons is regarded as a key mechanism leading to pathological discharges in vivo. As KCC2 maintains low intracellular

chloride concentrations, its reduced activity is associated with an altered GABAa receptor-mediated current equilibrium potential (EGABAa), which may lead to depolarizing/excitatory GABAergic transmission. Consistently, the pharmacological blockade of KCC2 in the isolated subicular network is sufficient to generate interictal-like spontaneous synchronization and transitions GABAergic inhibition generated by parvalbumin-expressing interneurons (PVs) into excitation. Here, I have used a more biologically relevant manipulation, which is the exposure of isolated subicular circuits to BDNF. In fact, increased levels of BDNF in the epileptic brain are believed to play critical roles for epileptogenesis, and the activity-dependent release of BDNF triggers the downregulation of KCC2 in neuronal membranes of mature neurons. I have taken advantage of PV-ChR2(H134R)-EYFP male and female mice to study PV-generated inhibitory postsynaptic potentials (IPSPs) in naïve vs BDNF-exposed (3 nM, 2hours, then recorded in ACSF) subicular slices. Pyramidal cells (PCs) were recorded in whole-cell current-clamp with a low-chloride intracellular solution with a predicted EGABAa of ~65 mV. IPSPs from PCs in naïve slices (held slightly above EGABAa) were consistently monophasic and hyperpolarizing with an integrated area of -211±62 mV*ms, which, as expected, was not affected by the pharmacological blockade of glutamatergic synaptic transmission with NBQX plus D-AP5 (-205±63 mV*ms, p=0.47, n=7 PCs). In contrast, IPSPs from BDNF-treated slices had a biphasic hyperpolarizing-depolarizing shape with an overall integrated area of +64±16 mV*ms, which was converted to -66±28 mV*ms (and full hyperpolarizing waveform) in the presence of NBQX and D-AP5 (p=0.016, n=7 PCs). In both naïve and BDNF-treated slices, IPSPs were completely blocked by the application of the GABAa receptor antagonist gabazine (p=0.002, n=10 PCs and p=0.02, n=7 PCs), thus indicating that, despite their different shapes, both IPSPs are critically dependent on GABAa receptor-mediated transmission. My interpretation is that BDNF treatment is sufficient to alter KCC2 function and leads to excitatory fast GABAergic transmission from (at least some) PVs that can recruit polysynaptic glutamatergic pathways generating the late depolarizing phase of the IPSP. These results have potential relevance for network signaling changes in the epileptic brain.

Disclosures: G. Maccaferri: None.

Poster

PSTR443: Network Dynamics and Interactions

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Topic: B.07. Network Interactions

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Title: Motor cortex manifolds for spontaneous behavior entail optimal dynamics

Authors: *A. FONTENELE[1], S. SOOTER[1], N. A. VASCONCELOS[2], K. NORMAN[3], S. GAUTAM[4], W. L. SHEW[5];

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Abstract: Sensory, cognitive, and motor functions emerge from the interaction of numerous neurons in brain circuits alongside bodily movements across various spatio-temporal scales. Determining the dynamical regime underpinning fundamental information processing capabilities is a perennial inquiry in systems neuroscience. A theory, heavily inspired by principles of critical phenomena, hypothesizes that the cerebral cortex operates close to a critical phase transition. This hypothesis offers an explanation for the observed complexity of brain dynamics and is biologically significant due to potential computational optimization near criticality. Recently, it was shown that the dominant neuronal modes (first few principal components), identified from the high-dimensional space during spontaneous behavior, exhibit fingerprints of optimal dynamics (i.e. criticality). However, the relationship between this manifold of optimal dynamics and behavior remains unclear. In this study, we address this gap by simultaneously recording spiking activity of many neurons in the mouse motor cortex and multiple detailed aspects of body movements. We asked two questions about how criticality relates to behavior. First, does the critical manifold encode behavior? Second, is proximity to criticality impacted by changes in behavior? We found that the critical manifold does encode many spontaneous behaviors. Second, we found that the motor cortex is closest to criticality for an intermediate level of body activity. Ultimately, we postulate that criticality underlies non-task-constrained behaviors, such as foraging, a mechanism that has been honed through the evolutionary process.

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Poster

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Topic: B.07. Network Interactions

Support: NIH Grant R15NS116742
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Title: Impaired tunability of brain state and motor dysfunction in a mouse model of Rett syndrome

Authors: *K. NORMAN[1], A. FONTENELE[2], S. SOOTER[3], S. GAUTAM[4], W. L. SHEW[5]; [1]Univ. of Arkansas, Fayetteville, Fayetteville, AR; [2]Physics Dept., Univ. of Arkansas Fayetteville, Fayetteville, AR; [3]Univ. of Arkansas Fayetteville, Fayetteville, AR; [4]Univ. of Arkansas, Fayetteville, AR; [5]Physics, Univ. of Arkansas, Fayetteville, AR

Abstract: Rett Syndrome (RTT) is a rare neurological disorder, caused by disrupted function of the MECP2 gene, resulting in impaired cognitive and motor functions. Previous studies suggest that although MECP2 has important functions throughout the body, the etiological origins of RTT-related dysfunction should be sought within the brain. However, it remains a mystery how neural population dynamics are altered in the RTT brain and how these alterations relate to motor dysfunction. Previous studies using an RTT mouse model point to abnormal correlations among firing rates of neurons. Here we hypothesize that such disrupted neural activity correlations could be caused by abnormal deviation from a particular dynamical regime, called criticality. Previous experiments and theory suggest that the brain tunes itself along a continuum of states nearby criticality, ranging from synchronized to desynchronized dynamics. Such tuning may take advantage of different computational advantages and tradeoffs near criticality. Here we performed electrophysiological recordings of many single units in the striatum of WT (n=4) and RTT (n=4) awake mice. The mice were head-fixed on a computer-controlled wheel with alternating rest and forced-run periods. We used a new theory-driven data analytic technique to assess proximity to criticality in a time-resolved way. In addition, we analyzed paw coordination during running and pupil size. We found that, during the forced run condition, RTT mice exhibited decreased paw coordination and tended to drag their hind paws more than WT mice. For both WT and RTT mice, we found the striatum is closer to criticality during rest periods than during the forced run periods. During forced run, the brain was tuned to a more desynchronized state. When comparing the deviation from criticality during the forced-run periods, we found that the WT mice were further away from criticality than RTT. Our results suggest that in RTT mice, neural dynamics are less tunable, unable to reach the desynchronized state. If the desynchronized state is beneficial for active behaviors like our forced run condition, then the inability to reach that state may contribute to decreased motor coordination and hypoactivity in RTT.

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Poster

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Topic: B.07. Network Interactions

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Title: The intrinsic and extrinsic regulation of fragile X messenger ribonucleoprotein on human hippocampal development

Authors: *J. XU[1], W. MA[2], S. YU[1], Y. LI[1], P. JIN[3], Z. WEN[1];
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Abstract: Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability and autism spectrum disorder, typically caused by CGG trinucleotide repeat expansion (>200 repeats) within the 5' UTR of the *FMR1* gene that leads to the silencing of *FMR1* and a complete loss of its encoding protein - fragile X messenger ribonucleoprotein (FMRP). FMRP is an RNA-binding protein that regulates translation, stability, transport, and/or editing of its mRNA targets. In FXS patients, cognitive deficits and behavior problems highlight a potential link between FMRP loss and hippocampus abnormality. Indeed, the hippocampus has been found to be enlarged in individuals with FXS at younger ages, suggesting an atypical developmental trajectory. While studies on *FMR1* knockout mice provide invaluable insights into the development and function of hippocampus in FXS, how FMRP loss affects human hippocampal development remains unknown. To address this question, we generated human hippocampal organoids from FXS patient derived- and healthy control derived-iPSCs. Through longitudinal transcriptomic profiling and cellular assays, we found that FXS hippocampal organoids exhibited increased neurogenesis at the early stage and decreased gliogenesis at the later stage. To determine whether there are hippocampal FMRP targets mediating this altered developmental trajectory, we performed eCLIP-seq to identify mRNA targets of FMRP at different stages. We found that FMRP transitions from interacting with genes involved in neurogenesis at the early stage to genes involved in gliogenesis at the later stage. Through single-cell transcriptomic profiling and bioinformatic analyses of the gene regulatory networks and cell-cell communications in hippocampal organoids, we proposed that FMRP regulates both intrinsic and extrinsic signaling through its direct gene targets, whose dysregulation upon loss of FMRP led to perturbed gene regulatory networks and disrupted cell-cell communications, ultimately resulting in neural network hyperexcitability in FXS hippocampal organoids that might be related to the hypersensitivity and hyperarousal in FXS patients. Taken together, our study not only delineates the molecular and cellular impacts of FMRP loss on hippocampus development, but also provides new insights into the regulatory role of FMRP and its direct gene targets during major developmental processes, which can be beneficial for the development of potential therapeutic strategies.

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Poster

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Title: Connectomic analysis shows that the non-human primate claustrum constitutes a unique hub structure of the cerebral cortex

Authors: *J. VEZOLI[1,2,3], Y. HOU[2], A. R. RIBEIRO GOMES[4], M. WANG[5,6,7], S. HORVÁT[8,2], Z. LUO[2], P. MISERY[2,3], C. LAMY[2,3], C. DEHAY[2,3], M.-M. POO[6], D. C. VAN ESSEN[9], M. ERCSEY-RAVASZ[10], Z. TOROCZKAI[11], K. KNOBLAUCH[2], Z. SHEN[6], H. KENNEDY[2,3,6];
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Abstract: The claustrum is telencephalic structure situated below the insula cortex. The wide-spread connectivity of the claustrum with the cortex suggests that it is involved in numerous higher-cognitive functions. Network analysis of brain networks identifies regions that are critical for efficient communication across the network and centrality analysis shows that these regions constitute hubs that play an important role in normal brain functions (van den Heuvel and Sporns, 2013). Our recent work on the transcriptome and connectome of the macaque claustrum reveals unique input output relations of the claustrum and cortex (Zheng et al., 2024). Here, we further explore these relations using graph theoretic techniques to explore the hub function of the claustrum. Surprisingly, we find that these cortical-claustral and intra-claustral connections do not obey the exponential distance rule, which is ubiquitous in the cortical inter-areal networks (Ercsey-Ravasz et al., 2013). Graph theoretic analysis of these findings show that the claustrum has very high centrality values and that it constitutes the unique hub of the cortex. These results suggest that the spatial embedding of the primate claustrum allows it to play a privileged role in facilitating the orchestration of rapid changes of brain state which we are currently exploring in non-human primate using multisite single unit recording simultaneously across the cortex and in the claustrum.
Contact: julien.vezoli@inserm.fr; henry.kennedy@inserm.fr.
References: Ercsey-Ravasz, M., Markov, N.T., Lamy, C., Van Essen, D.C., Knoblauch, K., Toroczkai, Z., and Kennedy, H. (2013). A predictive network model of cerebral cortical connectivity based on a distance rule. Neuron *80*, 184-197; van den Heuvel, M.P., and Sporns, O. (2013). Network hubs in the human brain. Trends Cogn Sci *17*, 683-696; Lei, Y., Liu, Y., Wang, M., Yuan, N., Ding, L., Zhu, Z., Wu, Z., Li, C., ⋯ Poo, M-M., Yao, J., Liu, L., Wei, W.,

Kennedy, H., Shen, Z. (2024) Single-cell spatial transcriptome atlas and whole-brain connectivity of the macaque claustrum. submitted

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Poster

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FWO-Flanders: G0C1920N
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Title: Effective connectivity of the Locus Coeruleus using combined microstimulation and functional magnetic resonance imaging in primates

Authors: *N. E. FITZGERALD[1], S. R. MURRIS[2], S. BOURET[3], W. VANDUFFEL[4]; [2]Lab. for Neuro- and Psychophysiology, [1]KU Leuven, Leuven, Belgium; [3]Paris Brain Inst. ICM, Paris, France; [4]Lab. For Neuro-And Psychophysiology, KU Leu, Leuven, Belgium

Abstract: The locus coeruleus (LC) is a small brainstem nucleus comprising 15,000 neurons in non-human primates and provides for all noradrenergic (NA) innervation in the brain. The LC can mediate both global and local modulatory effects throughout the brain, however, it is unknown how this is achieved. While attempts have been made to unveil the functional connectivity profile of this nucleus with the entire brain, none have been so direct as to stimulate the LC while recording functional MR images. The main objective of this study was the localization and subsequent electrical microstimulation of the LC, while performing functional MR imaging (fMRI) (1.25 isotropic voxels), to discern the effective connectivity profile of this area with the rest of the macaque brain. Using two male rhesus monkeys, we first identified the presumptive location of this nucleus using anatomical MR imaging. Thereafter, we targeted this area for electrophysiological recordings, which allowed us to functionally identify the nucleus with high precision and accuracy based on its known electrophysiological properties. Guided by these combined anatomical and electrophysiological properties, we subsequently paired electrical microstimulation (at 10, 50, and 100 Hz, 50 - 250 μA) with functional MR imaging while engaging the subjects in a passive fixation task. Using this ‘effective connectivity’ methodology, we were able to discern clear frequency- and amplitude-dependent effects throughout the primate brain. Our results, obtained with GLM and MVPA analyses, allowed us to identify key regions in

the macaque brain affected by the stimulation of this nucleus, including the visual cortex and cerebellum, and discern major activity patterns that are maintained across a variety of stimulation paradigms. We also characterized sub-regional activity patterns which depended on the frequency and amplitude of LC stimulation. This work provides key insights into how the LC encodes information and how it mediates its global effects. It also provides a framework for future investigations into the effective connectivity of the locus coeruleus and raises further questions as to the broad array of functional processes that the nucleus is involved in.

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Poster

PSTR443: Network Dynamics and Interactions

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.11/C4

Topic: B.07. Network Interactions

Support: NIH DIRP ZIAMH002797

Title: Neighborhood preferences in the unfolding of parabolic neuronal avalanches at cellular resolution in vivo

Authors: *T. F. SILVA, T. L. RIBEIRO, P. KELLS, D. PLENZ;
Section on Critical Brain Dynamics, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The spread of transient neuronal synchronization is a fundamental aspect underlying information processing in the brain in which selective participation allows neurons to form so-called cell assemblies. In the cortex, this spread has been captured in the local field potential as propagating waves (Rubino et al., 2006) and scale-invariant cascades in the form of neuronal avalanches (Petermann et al., 2009; Miller et al., 2019). Despite the high variability in the spatiotemporal synchronization of avalanches, quantified by powerlaws in their avalanche size and duration, the spread of LFP avalanches - in the average - obeys nearest-neighborhood principles similar to that of waves (Yu et al., 2014). It is currently not clear whether a similar neighborhood relationship is present in neuronal avalanches recorded with cellular resolution in vivo. Here we study the local spreading of synchronized neuronal firing in the frontal cortex of awake mice measured with 2-photon imaging using a chronically implanted window and microprism and the GECI jrGECO1a (n = 8 animals, 32 experiments). We analyzed ongoing spiking activity simultaneously recorded from ~200 neurons in superficial layers of the anterior-cingulate and medial prefrontal cortex for 30 min during quiet rest at a temporal resolution of 22 ms. Neuronal avalanches were separated into spatiotemporally resolved parabolic avalanches and finite-size constrained non-parabolic avalanches (Chapek et al., 2023). We calculated the average spatial distribution of near neurons at the initiation of an avalanches, corrected for the shuffled control if propagation was random. We found that a near-neighborhood preference in the

unfolding of parabolic avalanches, whereas such preference was reduced in parabolic avalanches. Our results confirm earlier reports for LFP avalanches and demonstrated that cascading neuronal synchronization in the form of neuronal avalanches is in line with local neighborhood preferences commonly known for cortical connectivity and spatial correlation functions.

Disclosures: T.F. silva: None. **T.L. Ribeiro:** None. **P. Kells:** None. **D. Plenz:** None.

Poster

PSTR443: Network Dynamics and Interactions

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.12/C5

Topic: B.07. Network Interactions

Support: NSFC82350710225

Title: Reboot of the VPMGlu->S1Glu pathway contributes to emergence of consciousness from anesthesia in mice

Authors: *J. HU[1], X.-J. SONG[2];
[1]Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Dept. of Med. Neurosci., SUSTech Ctr. for Pain Med. and Med. Sch., Southern Univ. of Sci. and Technol., Shenzhen, China

Abstract: General anesthetics can cause reversible loss of consciousness (LOC). Recovery of consciousness from anesthesia has historically been considered to be a purely passive process that occurs spontaneously as residual anesthetic levels fall below a critical level due to the gradual elimination of the anesthetic from the body. Recently, it has been shown that recovery from anesthesia is an active process driven by mechanisms that may be distinct from the induction of anesthesia. After the brain is forced into a minimum responsive state (MRS) by various anesthetics, ubiquitin-proteasomal degradation of K^+/Cl^- cotransporter 2 (KCC2) in the ventral posteromedial nucleus (VPM) of the thalamus serves as a mechanism for the brain to emerge from anesthesia and regain consciousness (Jiang-Jian Hu, et al., Nat Neurosci 2023). In the present study, we show in mice that emergence of consciousness from anesthesia can occur by rebooting VPM^{Glu} and $S1^{Glu}$ neurons and the $VPM^{Glu}\rightarrow S1^{Glu}$ pathway. Chemogenetic excitation or inhibition of the $VPM^{Glu}\rightarrow S1^{Glu}$ pathway, but not the $VPM^{Glu}\rightarrow S1^{GABA}$ pathway, respectively, attenuates or enhances anesthesia. Rebooting of VPM^{Glu} and $S1^{Glu}$ neurons and the $VPM^{Glu}\rightarrow S1^{Glu}$ pathway occurs independently of the pharmaceutical targets of the anesthetics used. The present study demonstrates that reboot of the $VPM^{Glu}\rightarrow S1^{Glu}$ pathway is critical for emergence from anesthesia and provides new insights into the neural circuits and molecular mechanisms underlying the process of consciousness recovery from unconsciousness.

Disclosures: J. Hu: None. **X. Song:** None.

Poster

PSTR443: Network Dynamics and Interactions

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR443.13/C6

Topic: B.07. Network Interactions

Title: Rapid plasticity of somatostatin-positive cortical interneurons during auditory training

Authors: *T. FREY[1], R. C. FROEMKE[2];
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Abstract: Rapid plasticity of somatostatin-positive cortical interneurons during auditory training

Authors
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Disclosure
T.M. Frey: none, R.C. Froemke: none

Abstract
Neuronal receptive fields of the cerebral cortex are highly plastic, and can be modified torepresent especially important variables or aspects of the sensory environment relating tobehavior responses (Froemke Annu Rev Neurosci 2015). A substantial literature hasdocumented several different cell types of local cortical interneurons, and cell-type-specificmanipulations of these different inhibitory cells can have certain consequences for networkfunction, plasticity, and behaviour (Kato et al. Neuron 2015, Kuchibhotla et al. Nat Neurosci2017, Fishell & Kepecs Annu Rev Neurosci 2020). Reward driven or other task-relatedcontingencies lead to changes in local inhibition responses; thus, impacting excitatory synapticplasticity and cortical reorganization. However, less is known about the patterns and specificlearning rules for various inhibitory cell types, or how the dynamics of inhibitory plasticity relateto changes of local excitatory neurons.Here we used two-photon imaging in head-fixed mice to record from somatostatin-positive(SST+) interneurons while animals performed a two-alternative forced-choice (2AFC) task(Martin et al. biorxiv 2023). Mice were progressively trained to differentiate between a single,center frequency (11-16 kHz) and non-center frequencies (by +/- 0.25-1.5 octaves from thecenter frequency) by licking left or right, respectively, for a water reward. We recorded fromSST+ neurons by injecting SST-Cre;Ai-9 mice (N=8) with a GCaMP8f virus to express withinall neurons of the left auditory cortex in males and females.We found that, during training on this auditory 2AFC task, SST+ neurons were recruited earlyin learning (in the 3-4 days of initial learning before animals' behavior began to improve). Theobserved time course of SST+ activation transformed over learning days. The SST activationpattern either occurred in form of sudden single-trial changes or slower new emergence oftone-evoked responses within a few trials. These changes could endure across trials, andSST+ responses were correlated with single trial performance, i.e., the tone-evokedresponses were qualitatively quite different on correct vs error trials.

Disclosures: T. Frey: None. **R.C. Froemke:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.01/Web Only

Topic: B.11. Neuro-Oncology

Support: JHU Provost's Undergraduate Research Award
JHU Albstein Research Scholarship

Title: B7 homolog 3 expression is associated with transcriptional reprogramming toward a malignant phenotype in glioblastoma

Authors: *A. LUO[1,3], N. MUNDHARA[1], S. SHARMA[1], K. CASELLA[1], D. PARÉ[1,4], E. BARABAN[2], C.-H. LUCAS[2], E. SHENDEROV[1];
[1]Oncology, [2]Pathology, Johns Hopkins Sch. of Med., Baltimore, MD; [3]Neurosci., Johns Hopkins Univ., Baltimore, MD; [4]Brooklyn Col., Brooklyn, NY

Abstract: B7 homolog 3 (B7-H3/*CD276*) is a transmembrane immunoregulatory protein that is highly and specifically upregulated in glioblastoma (GBM) among other human cancers, and efforts to target B7-H3 in clinical trials are currently underway. In addition to its putative role as an immune checkpoint ligand, B7-H3 has been shown to promote cancer cell metastasis and chemoresistance via non-immunological pathways. However, the precise molecular mechanisms of B7-H3-driven signaling remain incompletely understood. Here, we utilized immunohistochemistry, a cell model of CRISPR/Cas9-mediated B7-H3 deletion, and spatial transcriptomics to elucidate the functional role of B7-H3 in gliomagenesis. For each of 5 *IDH*-wildtype GBM tumor samples, 3 cores were identified by histological assessment to construct a tissue microarray (TMA). Staining by immunohistochemistry confirmed B7-H3 expression within 13 out of the 15 cores and across all 5 samples, localized to either the tumor cells or the tumor vasculature. To study the role of B7-H3 *in vitro*, we used CRISPR/Cas9 to establish a stable B7-H3 knock-out in the U87 MG cell line. Through bulk RNA sequencing, differential gene expression analysis, gene set enrichment analysis, and gene set variation analysis, we found that B7-H3 ablation led to significant metabolic alterations. In addition, when compared with Scramble reference control cells, B7-H3 knock-out cells exhibited a dysregulation of genes and pathways associated with cancer cell proliferation and migration. To build on these findings, we applied GeoMx whole-transcriptome digital spatial profiling to our TMA. Regions of interest segregated by high and low B7-H3 RNA expression preferentially associated with the more cellular tumor core and the more diffuse tumor periphery, respectively, implicating B7-H3 as a potential spatial biomarker. Altogether, our data suggest the involvement of B7-H3 in regulating fundamental cellular and molecular processes crucial for GBM tumor growth and progression. Further investigation may offer valuable insights for the development of targeted therapies against GBM.

Disclosures: A. Luo: None. **N. Mundhara:** None. **S. Sharma:** None. **K. Casella:** None. **D. Paré:** None. **E. Baraban:** None. **C. Lucas:** None. **E. Shenderov:** 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.; MacroGenics, Inc. F. Consulting Fees (e.g., advisory boards); GT Biopharma, Guidepoint Global, FirstThought, GLG, PathAI, CapitalOneSecurities, Forbion, Capvision, Insighter.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.02/C7

Topic: B.11. Neuro-Oncology

Support: MOST 110-2320-B-039-011

Title: The possible roles of GDF-15/GFRAL in glioblastoma progression: metastasis, immune escape, and macrophage polarization

Authors: *Y.-C. CHEN[1], W.-L. YEH[2];
[1]Inst. of Translational Med. and New Drug Develop., China Med. Univ., Taichung City, Taiwan; [2]Dept. of Biochem., Col. of Med., China Med. Univ., Taichung, Taiwan

Abstract: According to previous studies from our groups, growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory cytokine-1, is involved in tumor progression and metastasis. In 2017, several groups reported that GDNF family receptor alpha like (GFRAL) was a vital receptor of GDF-15 which mediates appetite and energy metabolism. Using both Gene Expression Profiling Interactive Analysis (GEPIA) and GEO database, we discovered that patients with brain tumor express higher GDF-15 level compared to normal samples. Moreover, increased GDF-15 expression possesses positive correlation with high mortality rate in glioblastoma (GBM). In this study, we aim to investigate the role of GDF-15 in GBM progression and communication between GBM and monocyte-derived macrophages. First of all, using both colony formation and transwell migration assay, recombinant GDF-15 protein was discovered to enhance U251 human GBM cells initiation and migration, respectively. In addition, recombinant GDF-15 protein induced GFRAL/RET (oncogene) pathway, leading to enhancement of downstream signals including phosphorylation of protein kinase B (AKT) and extracellular signal-regulated kinase (ERK). Next, we examined the relationship between several immune checkpoints using GEPIA database. Interestingly, GDF-15 gene expression was found to be positively correlated with several inhibitory immune checkpoints including CD276 (B7-H3) and CD274 (PD-L1). Since GDF-15 may also be expressed in macrophages, we further examined the relationship between U251-eGFP and THP1-derived macrophages. Using flow cytometry analysis, direct cell-cell contact between THP1-derived macrophages and U251-eGFP cells led to higher CD274 expression in both cells than cells cultured alone or in no-contact

transwell system. We also separated co-cultured U251-eGFP and THP1-derived macrophages by fluorescence-activated cell sorting, and we found that both chemokine ligand 2 (CCL2) and colony stimulating factor 1 (CSF1) were significantly increased in U251 cells, which also positively correlates with GDF-15 according to GEPIA database. Taken together, GDF-15/GFRAL mediated pathway may be critical in brain tumor progression and tumor-associated macrophage polarization.

Disclosures: Y. Chen: None. **W. Yeh:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.03/C8

Topic: B.11. Neuro-Oncology

Support: 316833 CONAHCyT
321677 CONAHCyT

Title: Inhibition of WNT- and TBK1-dependent signaling induces changes in viability, cell cycle progression and NF-kB activity in human glioblastoma cell lines

Authors: *I. CONTRERAS[1], G. CONTRERAS CHÁVEZ[2], L. Á. ZAPI-COLÍN[3], V. MARIN ZULUAGA[4], J. A. ESTRADA[5];
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Abstract: The aim of this study is to determine the effects of pharmacological blockade of WNT and TBK1 signaling pathways on the cell cycle, viability, and NF-kB activation in U87MG and A172 human glioblastoma cell lines. U87MG and A172 cells were cultured with WNT or TBK1 specific inhibitors IWP12 and BX795, at 0.1-10 μM concentrations for 24-72 h. Total and phosphorylated (p) NF-kB p50 and p65 protein expression were assessed by western blot analysis, compared to untreated controls. Cell cycle progression and viability were evaluated by flow cytometry and spectrophotometry, respectively. Change fold compared to untreated cells (arbitrary unit of 1.0) was used for WB analysis. Preliminary results showed decreased (p)p50 and (p)p65 protein expression in both cell lines after BX795 treatment. Statistically-significant differences for (p)p50 were observed after 72 h with all concentrations (0.1 μM (0.68 ± 0.04); 1 μM (0.66 ± 0.04), 5 μM (0.41 ± 0.01), 10 μM (0.41 ± 0.02); $p \leq 0.001$). Meanwhile, (p)p65 showed a significantly reduced expression after treatment with 5 μM after 72 h (0.60 ± 0.01) and 10 μM (0.60 ± 0.04) BX795; $p \leq 0.001$). In A172 cells, a similar phenomenon was observed since both (p)p50 (5 μM (0.33 ± 0.01) and 10 μM (0.24 ± 0.06)) and (p)p65 expression (5 μM (0.32 ±

0.02) and 10 µM (0.31 ±0.08)) were significantly reduced after 72 h treatment with BX795 ($p \leq 0.001$). No changes in the expression of either protein were observed with IWP12 treatment. Regarding the cell cycle, 24 h with 10 µM BX795 induced a decrease in the frequency of U87MG cells at G0/G1 phase (24.81 ± 2.8% vs. 54.42 ± 2.3% (treated vs. control)) and an increase in the frequency of S/G2/M cells (75.19 ± 2.8 vs. 45.58 ± 2.3%; $p<0.001$). In A172 cells, 24 h with 1 µM IWP12 reduced the frequency of cells at G0/G1 (46.03 ± 1.38% vs. 69.83 ± 0.65%) and increased the frequency of cells at S/G2/M (53.97 ± 1.4% vs. 30.17 ± 0.54%). Additionally, 10 µM BX795 at 24 h induced a decrease in the frequency of G0/G1 cells (46.93 ± 0.88% vs. 69.83 ± 0.65%; $p<0.001$), with a corresponding increase in the frequency of cells at S/G2/M (53.07 ± 1.2% vs. 30.17 ± 0.72%; $p<0.001$).Finally, a reduction in cell viability in both cell lines was observed after treatment with both inhibitors at 24-72 h, showing the greatest effect with 10 µM BX795 at 72 h (3.92 ± 0.88% vs. 100% (control group)) in U87MG cells and (13.6 ± 0.40% vs. 100%) in A172 cells.Together, our preliminary results show that pharmacological blockade of WNT and TBK1, leads to changes in the cell cycle and viability of two human glioblastoma cell lines, relating with reduced NF-kB p50 and p65 activity.

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Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.04/C9

Topic: B.11. Neuro-Oncology

Support: 2023 Student Endeavors Grant
Neuroscience Program at CMU
College of Medicine at CMU
Department of Chemistry and Biochemistry at CMU
John G. Kulhavi Professorship in Neuroscience
E. Malcolm Field and Gary Leo Dunbar Endowed Chair in Neuroscience at CMU

Title: Evaluating the therapeutic effects of delivering CRISPR/Cas9 and small interfering RNA molecules via G4-70/30 Polyamidoamine dendrimer nanomolecules on human glioblastoma cells in vitro.

Authors: *C. NOE[1], A. POUDEL[2], J. EVERS SMITH[3], B. SRINAGESHWAR[2], J. BAKKE[1], G. L. DUNBAR, Sr.[4], J. ROSSIGNOL[5];
[1]Central Michigan Univ., Mount Pleasant, MI; [2]Neurosci., Central Michigan Univ., Mount Pleasant, MI; [3]Neurosci., Central Michigan Univ. Undergraduate Program In Neurosci., Mt. Pleasant, MI; [4]Psychology/Program in Neurosci., CENTRAL MICHIGAN Univ., MOUNT PLEASANT, MI; [5]Col. of Med., Central Michigan Univ., Mount Pleasant, MI

Abstract: Glioblastoma (GB) is the most common and aggressive central nervous system tumor, with a 15-month median survival time after diagnosis. There has never been a cured case reported, stressing the need for new GB treatments. One promising novel GB treatment involves targeting the *AVIL* gene, the overexpression of which is essential for the survival, migration, and invasion of GB cells. In this study, we evaluated the efficacy of CRISPR/Cas9 and small interfering RNA (siRNA) therapy *in vitro*, which target the *AVIL* gene and *AVIL* mRNA, respectively. The efficacy of these gene therapies is limited by poor cellular uptake and low stability. Therefore, we used Generation 4 (G4)-70/30 Polyamidoamine (PAMAM) dendrimer nanomolecules, which improve the stability and bioavailability of encapsulated treatments such as CRISPR/Cas9 and siRNA therapy. Encapsulating siRNA molecules in these dendrimers yielded a stable complex. RT-PCR data showed that siRNA treatment using the RNAiMAX transfection reagent conferred *AVIL* knockdown in both HEK 293 and U87 cells. Treatment with the dendrimer-siRNA complex produced *AVIL* knockdown in U87 cells to a lesser degree. We are working to further optimize the dendrimer-siRNA treatment to confirm these results. CRISPR/Cas9 transfected U87 cells were analyzed for gene knockout via Sanger sequencing and protein expression via Western blotting. Sanger sequencing of transfected U87 cells showed 55% *AVIL* gene knockout after three days post-transfection. Western blot analysis of CRISPR/Cas9-treated U87 cells revealed reductions in the proteins p92 and FOXM1, which are downstream targets of the *AVIL* gene. However, Western blot analysis of siRNA-treated U87 cells revealed reductions in p92 but not FOXM1, suggesting that CRISPR/Cas9 may be more effective in treating the U87 model of GB than siRNA treatment. The preliminary data gathered in this study suggests that *AVIL* gene inhibition is a potential treatment option for GB. We aim to confirm this by further replicating these treatments and *AVIL* knockdown analysis methods.

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Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.05/C10

Topic: B.11. Neuro-Oncology

Title: Unraveling Transcriptomic Alterations Induced by Oncogene CTCFL Overexpression in Human Glioblastoma

Authors: *S. PLATA BURGOS[1], G. RAMIREZ MEJIA[2], E. SOTO-REYES[3];
[1]Univ. Nacional Autónoma de México, Mexico City, Mexico; [3]Natural Sci., [2]Univ. Autónoma Metropolitana - Cuajimalpa, Mexico City, Mexico

Abstract: Glioblastomas are the most aggressive and common primary tumors of the central nervous system, characterized by poor survival rates and high mortality. Multiple molecular mechanisms contribute to the formation and proliferation of these neoplasms, including

epigenetic mechanisms.The nuclear epigenetic factor CTCF, a zinc finger protein, plays a pivotal role in chromatin organization and demonstrates aberrant regulation in multiple diseases, including cancer. Its paralog, CTCFL, and associated protein BORIS, have been identified as overexpressed in several cancer types, and have been associated in tumor aggressiveness by promoting proliferation and stemness, in several cases. Previous reports have suggested a potential competition between CTCF and CTCFL for DNA binding sites, potentially leading to widespread dysregulation of gene expression. In this study, we conducted bioinformatic analyses of high-throughput ChIP sequencing data and high-throughput RNA public data from the The Cancer Genome Atlas Project to investigate the potential role of CTCFL as a transcription factor for genes associated with cancer.Our findings reveal that BORIS may regulate several cancer biomarkers and genes such as ALDH1A3, and SIX1. Ontology underscores their involvement in molecular mechanisms such as stemness and vascularization, processes that contribute to tumor aggressiveness. Furthermore, we observed an inverse expression pattern between CTCF and CTCFL, suggesting a potential competition for DNA binding sites. Overall, our findings shed light on BORIS's regulatory role in cancer biology, providing valuable insights into glioblastoma pathogenesis and aggressiveness. Furthermore, our findings suggest the potential utility of BORIS as a biomarker in glioblastoma research, warranting further investigation into its clinical relevance.

Disclosures: S. Plata Burgos: Other; Scholarship from CONACyT for the study. **G. Ramirez Mejia:** None. **E. Soto-Reyes:** 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.; Consejo Nacional de Ciencia y Tecnología (CONACyT) Fondo CB-SEP-CONACyT (284748, PROMED 250690) ,Soto-Reyes, E., the Natural Science Department at UAM Cuajimalpa (DCNI--07-243-23).

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.06/C11

Topic: B.11. Neuro-Oncology

Support: NSF EFRI/2129617

Title: Extracellular matrix stiffness within glioblastoma tumor affects characterization and protein content of extracellular vesicles

Authors: *C. PAYNE;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Glioblastoma (GBM) is a devastating brain tumor that is highly aggressive and invasive form of cancer that is characterized by poor patient prognosis. Changes within the

microenvironment have been shown to affect GBM tumor invasion. Previous research has shown that stiffening of the extracellular matrix (ECM) enhances cell migration and proliferation. Extracellular vesicles (EVs) have been shown to facilitate tumor growth and invasiveness through their ability to carry proteins and metabolites throughout the tumor microenvironment. The purpose of this study was to elucidate the effect ECM stiffness had on the concentration, size, and cargo of the EVs thereby potentially creating a more pro-tumorigenic microenvironment. To do this, we seeded U87MG cells on premanufactured collagen coated on hydrogels of 100Pa, 4kPa, and 25kPa stiffness and 48 hours post seeding collected and ultracentrifuged media to collect the released EVs. We then conducted nanotracking analysis (NTA) and proteomics to assess changes in EVs resulting from ECM stiffness. NTA indicated that there was an increase in number of EVs with stiffness, with a 2.6x increase between the number of EVs released from GBM cells cultured on 100Pa hydrogels versus 25kPa cultured GBM cells. but the size of the ECM remained constant. Western blot analysis also showed an increase in the presence of CD9 and CD63, two tetraspanin proteins used as biomarkers for EVs. Proteomics identified three proteins, YWHAG, Titin, and TAGLN2, that significantly changed with stiffness. These proteins have implications in cell signaling, movement, morphology, and cell cycle regulation. This study shows that ECM stiffness affects not only the number of EVs in the microenvironment but also the protein content potentially resulting in a more pro-tumorigenic microenvironment in areas of increased ECM stiffness.

Disclosures: C. Payne: None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.07/C12

Topic: B.11. Neuro-Oncology

Support: NIH Grant OD023689

Title: Versatile genetic perturbation approach to understand tumor-immune interactions in human glioblastoma

Authors: *S. NEHME[1,2,3], H. ALNAIB[1,2,3], T. HARA[1,2,3], D. MUKHAMEJANOVA[1,2,3]; [1]Univ. of Michigan, Ann arbor, MI; [2]Neurosurgery, University of Michigan Medicine, Ann arbor, MI; [3]BioInnovations in Brain Cancer, Biointerfaces Institute, Ann arbor, MI

Abstract: The mechanism by which macrophages induce a transition of glioblastoma (GBM) cells into a mesenchymal (MES)-like state remains unclear. Macrophages produce a cytokine known as Oncostatin M (OSM), which has been shown to facilitate this transition in GBM cells. Although the involvement of OSM is recognized, the precise mechanisms and potential additional factors are still uncertain. In this study, previous work utilized single-cell RNA sequencing (scRNA-seq) to analyze GBM subtype expression in various cellular states. Human

GBM cells (MGG23) were treated with macrophage-derived ligands for 24 hours and assessed for glioblastoma states via CD24 and CD44 markers with flow cytometry. Additionally, we employed the Neon electroporation system using CRISPR/Cas9 to knock out the OSM gene in human macrophages (U937), achieving high transfection efficiency. Single-cell cloning by limiting dilution produced putative OSM knockout (KO) clones, which were assessed using PCR and gel electrophoresis. We plan to perform Sanger sequencing on clones suspected of being knocked out to ascertain the precise DNA sequence at the OSM locus. Upon confirming a successful knockout, the modified clones will be co-cultured with glioblastoma cells to investigate their interactions in vitro. Future studies will further elucidate how OSM contributes to a heterogeneous microenvironment in mesenchymal-like GBM.

Disclosures: S. Nehme: Other; Undergraduate Student. **H. Alnaib:** Other; Undergraduate Student. **T. Hara:** A. Employment/Salary (full or part-time):; Full time. Other; Principal Investigator. **D. Mukhamejanova:** Other; Visiting Undergraduate Student.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.08/C13

Topic: B.11. Neuro-Oncology

Support: CONAHCYT CB-SEP-CONACYT (284748, PROMED 250690)
UAM Cuajimalpa, Natural Science Department (DCNI-07-243-23)

Title: The Brother of the Regulator of imprinted Sites (BORIS) potentially regulates the expression of genes associated to glioblastoma pathogenesis

Authors: *G. RAMIREZ MEJIA[1], S. PLATA BURGOS[2], E. SOTO-REYES[1];
[1]Univ. Autónoma Metropolitana - Cuajimalpa, Mexico City, Mexico; [2]Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Various studies on cancer suggest that cancer cells undergo genetic and epigenetic changes that disrupt gene expression. These changes are aimed at promoting proliferation, cell survival, apoptosis resistance, evasion of immune response, and angiogenesis, among others.
It has been reported that Brother of the Regulator of Imprinted Sites (BORIS) may compete with its paralog, CTCF, leading to impaired gene expression. BORIS has been associated with different tumors, the studies suggest that it may confer stemness characteristics to cancer cells, thereby contributing to cancer formation and progression. Consequently, BORIS has been proposed as a potential cancer marker.
In the central nervous system, the most aggressive form of cancer is glioblastoma (GBM), believed to arise from the transformation of glial cells. BORIS has been implicated in the invasive capacity of GBM cells, although the precise mechanism remains unclear. Thus, the aim of this study is to investigate whether BORIS regulates gene expression that contributes to the

tumorigenic capacity of glioblastoma cells.
To achieve this, we examined the expression levels of BORIS and CTCF in T98G and U87MG cells. Additionally, we analyzed the binding of BORIS to chromatin using chromatin immunoprecipitation (ChIP) followed by sequencing to identify BORIS binding sites on the genome. Subsequently, we conducted gene ontology analysis to determine the functions of the genes potentially regulated by BORIS.
Our findings reveal an inverse expression pattern between BORIS and CTCF, suggesting potential competition for gene binding sites. ChIP-seq analysis indicates that BORIS predominantly binds to promoter regions, while gene ontology analysis suggests that BORIS may regulate genes involved in developmental processes, anatomical morphogenesis, various cellular functions, and cell communication. Some of those processes could explain how glioblastoma cells acquire stemness characteristics.
Overall, our results suggest that BORIS may regulate the expression of genes associated with different aspects of glioblastoma pathogenesis. Consequently, BORIS could serve as a potential marker for glioblastoma aggressiveness.

Disclosures: G. Ramirez Mejia: None. **S. Plata Burgos:** None. **E. Soto-Reyes:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

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Topic: B.11. Neuro-Oncology

Support: NSF No. EEC-1648035
NIH Grant 1R21NS119167-01

Title: Disrupting Akt/β-catenin signaling suppresses glioma stem cell growth and tumor progression in immunocompetent mice

Authors: *M. SARKAR[1,2], N. GONSALVES[1,2], A. DAVARZANI[3,1], E. MITCHELL[4], S. RAMASUBRAMANIAN[1,2], A. SINGH[6], L. KARUMBAIAH[1,5,2], S. L. STICE[5,6,1,2];
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Abstract: Glioblastoma Multiforme (GBM) is an invasive brain tumor, where 55% of patients exhibit protein kinase B (AKT) hyperactivation within phosphatidylinositol 3-kinase (PI3K)/AKT signaling axis. Wingless (Wnt)/β-catenin activity is also high in some GBM cells. PI3K/AKT and Wnt/β-catenin signaling pathways drive GBM tumor aggressiveness by controlling glioma stem cells (GSC) survival, proliferation, metabolism, angiogenesis, and invasion. A critical knowledge gap exists regarding the crosstalk between the PI3K/AKT and

Wnt/β-catenin pathways in GBM. The effect of PI3/AKT and Wnt/β-catenin inhibitors on GBM progression in immunocompetent animal models remains unexplored. We hypothesize that targeting AKT and β-catenin, two central regulatory components of the PI3K/AKT and Wnt/β-catenin signaling pathway, will inhibit GBM cell growth and tumor progression. Mouse glioma cells (CT-2A) and patient-derived human glioma stem cells (N08-30) were treated with or without AKT (MK-2206) and β-catenin (iCRT3) inhibitor and examined for cell viability, apoptosis, β-catenin transcriptional activity, Wnt gene expression and protein phosphorylation. Luciferase expressing CT-2A cells were intracranially inoculated in C57BL/6J mice (vehicle n=9 and treatment n=11) (Day 0). Tumor uptake was confirmed by bioluminescence (BLI) imaging on Day 7 following an intraperitoneal (IP) D-luciferin injection (150mg/kg body weight). Mice were then randomized into two groups: one receiving daily IP injections of the AKT inhibitor MK-2206 (100mg/kg body weight) and vehicle control group receiving 20% β-captisol. Tumor size was monitored every 7-days by BLI imaging. At the study endpoint, magnetic resonance imaging (MRI) was performed followed by tumor tissue collection for histochemical analysis. Glioma cell (CT-2A and N08-30) viability and proliferation was reduced dose dependently with MK-2206 and iCRT3. However, MK-2206 was more potent at reducing cell viability and proliferation ($p=0.0021$), inducing apoptosis ($p=0.002$) and inhibiting Wnt gene expression ($p=0.01$) than iCRT3. The tumor size (BLI signal) of the MK-2206-treated group was significantly reduced ($p=0.0381$), along with pAKT(Ser473) ($p=0.0065$) and pGSK-3β(Ser9) ($p=0.0061$) levels in tumor tissue, compared to control. Terminal MRI and hematoxylin and eosin staining of tumor tissue reconfirmed the BLI results of tumor size reduction following MK-2206 treatment. MK 2206 outperformed iCRT3 efficacy *in vitro,* and suppressed GBM progression, *in vivo*. MK-2206 is a promising therapeutic candidate for treating glioblastomas, where AKT and β-catenin signaling is upregulated.

Disclosures: M. Sarkar: None. **N. Gonsalves:** None. **A. Davarzani:** None. **E. Mitchell:** None. **S. Ramasubramanian:** None. **A. Singh:** None. **L. Karumbaiah:** None. **S.L. Stice:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.10/C15

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Author's research is funded by a company that produces a product or service related to the work being reported.

Title: Reveal the Heterogeneity of Glioblastoma and Other Tumors Using High-Plex Imaging Mass Cytometry Empowered by Whole Slide Imaging Modes

Authors: Q. RAZA[1], T. D. PFISTER[1], J. CHWEE[1], C. LOH[1], D. HOWELL[2], N. PARSOTAM[1], J. PEMBERTON[1], N. ZABINYAKOV[1], ***C. LOH**[1];

[1]Standard BioTools Canada Inc., Markham, ON, Canada; [2]Standard BioTools Inc., San Francisco, CA

Abstract: Gaining spatial insights into the cellular composition of tumor tissue has tremendous potential to inform clinicians and researchers about mechanisms behind spatial predictors of treatment success and disease etiology and progression. Imaging Mass Cytometry™ (IMC™) is a high-plex spatial biology imaging technique that enables deep characterization of the diversity and complexity of the tumor microenvironment (TME). IMC supports detailed assessment of cell phenotype and function using 40-plus metal-tagged antibodies simultaneously on a single slide without artifacts associated with fluorescence-based spectral overlap, tissue autofluorescence, multiple acquisition cycles and tissue degradation. We developed whole slide imaging (WSI) modes that enable a streamlined and improved workflow for high-throughput tissue analysis. Preview Mode (PM) samples the entire tissue at predefined spacing to rapidly capture a low-resolution image of all expressed markers in an antibody panel. PM generates tissue images in minutes to enable marker-guided ROI placements while leaving the stained tissue intact for high-resolution Cell Mode (CM) imaging. Tissue Mode (TM) rapidly acquires images of the whole tissue at lower resolution at a quality that can be used for quantitative analysis of the tissue's spatial biology. Specifically designed for high-throughput applications, TM in combination with a 40-slide loader for the Hyperion XTi™ Imaging System permits automated and continuous imaging of over 40 large tissue sections (400 mm^2 per tissue) per week. We showcase the application of WSI modes using the Human Immuno-Oncology IMC Panel, 31 Antibodies. The 31-marker base panel was combined with additional Maxpar® antibodies to create a 41-marker panel that expands the ability to conduct comprehensive high-plex tumor and immune cell profiling. Tumor tissue microarrays and whole tumor tissue sections, including glioblastoma tissue, were stained and imaged. Single-cell analysis of selected ROIs acquired using CM successfully provided quantitative analysis of a sample's spatial biology. In parallel, TM on whole tumor sections followed by pixel-clustering analysis provided a spatially resolved quantitative assessment of specific tumor and immune compartments of the TME. This work demonstrates the expanded capabilities of IMC and establishes it as a reliable high-plex spatial biology imaging technology with high-throughput imaging capabilities ideally suited for future translational and clinical applications. For Research Use Only. Not for use in diagnostic procedures.

Disclosures: Q. Raza: A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **T.D. Pfister:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard

BioTools. **J. Chwee:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); uthor has ownership interest with Standard BioTools. **C. Loh:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **D. Howell:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **N. Parsotam:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **N. Zabinyakov:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **C. Loh:** A. Employment/Salary (full or part-time):; Full time employee of Standard BioTools Canada Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Author's research is funded by a company that produces a product or service related to the work being reported.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.11/C16

Topic: B.11. Neuro-Oncology

Title: Nuclear NAD+ synthase NMNAT1 contributes to nuclear atypia and promotes glioma growth

Authors: *J. LIU[1], Y. ZHU[2], R. G. ZHAI[3];
[1]Univ. of Chicago, Chicago, IL; [2]Mayo Clin., Rochester, MN; [3]Neurol., Univ. of Chicago, Chicago, IL

Abstract: Glioma is a malignant primary brain tumor with poor prognosis and short survival. Targeting NAD^+ biosynthesis within tumors has emerged as a potential therapeutic strategy, yet the modest effectiveness observed in clinical settings indicates an incomplete comprehension of the involved biological mechanisms. Nuclear atypia, aberrations in the size and shape of the nucleus, is widely observed in cancer cells and often considered as a distinctive feature in tumor diagnosis, however, the molecular underpinnings are still to be fully elucidated. In this study, we carried out high-resolution imaging analysis of glioma patient tissue samples and identified an increased expression of nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1), the nuclear NAD^+ synthesizing enzyme in high-grade gliomas, which was associated with nuclear atypia. We employed a *Drosophila* model of glial neoplasia to explore the genetic involvement of NMNAT in the growth and development of glioma in vivo. Further mechanistic studies in human glioma cell lines suggest that NMNAT1 interferes with the integrity of the nuclear lamina through alterations of lamin A/C distribution. This study uncovers a novel mechanism, underscoring the contribution of the NAD^+ biosynthetic enzyme NMNAT1 to the exacerbation of glioma aggressiveness through the facilitation of nuclear atypia.

Disclosures: J. Liu: None. **Y. Zhu:** None. **R.G. Zhai:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.12/C17

Topic: B.11. Neuro-Oncology

Support: CBF2023-2024-1982

Title: Phototoxic effect from UV light irradiation of folic acid functionalized TiO_2-ZnPc nanoparticles on glioma cells. A preliminary study

Authors: *E. ORTIZ[1], M.-R. MANRIQUEZ[3], C. RODRÍGUEZ-PÉREZ[2], J. GUSTAVO[4];
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Abstract: TiO_2 nanoparticles were prepared, combined with a zinc phthalocyanine and functionalized with folic acid to obtain a nano-photosensitizer for its targeted application in photodynamic therapy against glioblastoma cancer cells. The nanoparticles were also characterized by various physicochemical techniques such as X-ray diffraction, transmission electron microscopy, infrared and UV-Vis spectroscopy. An in vitro toxicity assay was performed using the MTT method and C6 cell line. A preliminary phototoxicity test was performed by irradiating the nanoparticles previously incubated with the C6 cells with a 385 nm LED lamp for 15, 30 and 60 min. Successful folic acid functionalization and excellent combination with phthalocyanine were also achieved. The characterization results showed that a mixture of anatase-amorphous phases make up the structure of the nanoparticles. The UV-Vis spectrum of functionalized and combined TiO_2 nanoparticles showed a new signal at 640 nm, which is due to the interaction between TiO_2 and phthalocyanine. The different TiO_2 nanoparticles resulted to be non-toxic to C6 cells at all concentrations used compared to cis-Pt treatment. Preliminary studies on photoactivation of nanocarriers with ultraviolet light resulted in a marked reduction in the viability of C6, which was incremental depending on the concentrations of titania nanoparticles. These preliminary results allow us to postulate that TiO_2 nanoparticles are biocompatible and are activated only by light irradiation to generate charge separation and produce ROS species. However, it is necessary to make more studies using different glioma cell lines and to determine the mechanism of cell death.

Disclosures: E. Ortiz: None. **M. Manriquez:** None. **C. Rodríguez-Pérez:** None. **J. Gustavo:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.13/C18

Topic: B.11. Neuro-Oncology

Support: DFG, German research foundation, FOR 2591

Title: Voluntary Wheel Running in a Rat Model of Intracranial Glioma: Assessment in Single and Group Housing

Authors: *A. OTTLEWSKI, J. KRAUSS, K. SCHWABE;
Hannover Med. Sch., Hannover, Germany

Abstract: Animal models of intracranial tumor formation are essential for the development and improvement of novel therapeutic approaches. Likewise, adequate and objective parameters for severity assessment as well as humane endpoint determination of laboratory animals are fundamental for ethical and legal reasons. Voluntary wheel running (VWR) has been identified as a novel and robust parameter for severity classification. Therefore, we implemented VWR in our rat model of brain tumor. We here evaluated VWR behavior in addition to daily-recorded body weight and clinical scoring after neurosurgical interventions of tumor cell injection and resection, as well as humane endpoint detection after tumor regrowth. For this study, male BDIX rats were either single-housed (n=14) in wheel-equipped cages or group-housed (n=6) in a large cage assembly (three Makrolon type IV cages connected by tubes) equipped with running wheels, where rats could be identified by a subcutaneously placed RFID chip. Under general anesthesia, both groups received stereotactic injection of glioblastoma BT4Ca-cells into the frontal cortex. Additionally, animals kept in groups were implanted with a guide cannula for local vehicle administration in the emerging tumor region. After eight days, single housed rats received microsurgical resection of the resulting tumor. Body weight, clinical score and VWR were monitored daily until the humane endpoint criterion of sudden weight loss and deteriorated clinical score was reached.In single-housed rats, body weight was slightly but significantly reduced after cell injection and tumor resection ($p<0.05$), along with reduced VWR ($p<0.05$) while clinical state remained unimpaired. On the day of the humane endpoint, sudden weight loss and deteriorated clinical score were associated with almost no VWR ($p<0.05$). Analysis of group-housed rats showed that decreased VWR was accompanied with weight loss ($p<0.05$) after tumor cell implantation and before reaching the humane endpoint, accompanied by degraded clinical score. Together, the monitoring of VWR enhances an objective severity assessment of neurosurgical approaches in rat models with intracranial tumor formation, including the determination of humane endpoints both in single and grouped housed animals.

Disclosures: A. Ottlewski: None. **J. Krauss:** None. **K. Schwabe:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.14/C19

Topic: B.11. Neuro-Oncology

Support: CCS 708237
CIHR Canada Graduate Scholarship

Title: Systemic Chemotherapy induces structural changes in cerebral vessels in the hippocampus

Authors: *M. SHAHWAN[1], D. RIWA[1], M. HIRASAWA[2];
[1]Div. of Biomed. Sci., Mem. Univ., St. John's, NL, Canada; [2]Div. of Biomed. Sci., Mem. Univ., St John's, NL, Canada

Abstract: Introduction: Chemotherapy, the primary option to treat cancer, has numerous neurotoxic side effects such as cognitive impairment known as chemobrain, characterized by impaired memory. Chemobrain is prevalent in 16-75% of cancer patients and can last for decades. 5-Fluorouracil (5FU), an antimetabolite chemotherapy agent for many cancers, has been shown to impair hippocampus-dependent cognitive functions in humans and animal models. This study investigated structural alterations in hippocampal vasculature and associated glial cells essential for maintaining the blood brain barrier (BBB). **Methods**: 8-week old male C57BL/6 mice received 4 weekly i.p. injections of 5FU (75 mg/kg) or saline (control) and sacrificed 7d post-injection. Cerebral vessels within the hippocampal CA1 were visualized using FITC-tomato lectin for endothelial cells (ECs) and immunohistochemistry for astrocytic marker GFAP, or by electron microscopy (EM). **Results**: At the light microscopic level, the area fraction of GFAP in the CA1 region of the hippocampus was significantly increased by 5FU treatment. Vessels surrounded by astrocytic endfeet were assessed by comparing the diameter of GFAP to the diameter of lectin stained ECs. The GFAP to lectin ratio was increased with 5FU treatment, suggesting thickening of astrocytic endfeet around vessels. Furthermore, our EM results show swollen astrocytic endfeet around a compressed vessel following 5FU treatment compared to saline controls, confirming our IF results. In addition, an increase in microvilli and vacuoles were observed in ECs after 5FU. **Conclusion**: Collectively, our study suggests that 5FU induces abnormalities in cerebral vessels in the hippocampus, including microvilli and vacuoles in ECs, and swelling of astrocyte endfeet. These changes persist even after the 5FU elimination period, which suggest prolonged functional impairment of the BBB that may contribute to chemobrain.

Disclosures: M. Shahwan: None. **D. Riwa:** None. **M. Hirasawa:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.15/C20

Topic: B.11. Neuro-Oncology

Title: Papillary tumor of the pineal gland: series of four clinical cases

Authors: *J. G. ROJO ALFARO[1], M. TENA SUCK[2], G. GONZALEZ-GARIBAY[3], L. MARIN-CASTAÑEDA[4], C. MARTÍNEZ ZAMORA[2], H. M. ROMO-PARRA[5], A. LOPEZ, Sr.[6], S. VIDAL[2];
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Abstract: The papillary tumor of the pineal region (PTPR) is a rare neuroepithelial tumor originating from specialized ependymocytes. It primarily affects structures within the pineal region, including the pineal gland, epithalamus, quadrigeminal cistern, and posterior wall of the third ventricle. Here, we present a series of four cases characterized by symptoms associated with obstructive hydrocephalus, such as headaches, seizures, visual disturbances, gait disturbances, and Parinaud syndrome. Imaging studies revealed lesions in the pineal region, prompting surgical intervention. Histopathological examination, including biopsy and intraoperative analysis, confirmed the diagnosis of PTPR. Despite advancements, the etiology and pathogenesis of PTPR remain incompletely understood, warranting further research to refine management strategies.

Disclosures: J.G. Rojo Alfaro: None. **M. Tena Suck:** None. **G. Gonzalez-Garibay:** None. **L. Marin-Castañeda:** None. **C. Martínez Zamora:** None. **H.M. Romo-Parra:** None. **A. Lopez:** None. **S. Vidal:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.16/C21

Topic: B.11. Neuro-Oncology

Title: Neural Network Modularity in Survivors of Acute Lymphoblastic Leukemia Compared to Matched Healthy Controls

Authors: *J. TANNER[1], W. REDDICK[2], L. JACOLA[1], K. R. KRULL[1];
[1]Psychology and Biobehavioral Sci., [2]Diagnos. Imaging, St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Background: Identifying mechanisms of neurocognitive impairment in survivors of childhood acute lymphoblastic leukemia (ALL) may help guide targeted interventions. Brain network modularity, a connectivity metric from functional magnetic resonance imaging, has been associated with neural plasticity and recovery from neurocognitive impairment. We aimed to describe network modularity in ALL survivors compared to healthy controls. Methods: Neuroimaging data were acquired from survivors treated on a single contemporary chemotherapy protocol (N=130, 13.6y [8.2-21.2] at assessment, 10.9y [5.6-18.6] at diagnosis, 73% female). Healthy controls were propensity matched 2:1 from the Adolescent Brain Cognitive Development study (N=260, 14.1y [8.1-21.7] at assessment, 78% female). Neuroimaging preprocessing and first-level analyses were performed in the CONN Toolbox using 232 ROIs defined in the Power atlas. Network modularity was calculated with the Brain Connectivity Toolbox after binarizing the whole-brain correlation matrix at link densities 1% to 50%. At each link density, a generalized linear model evaluated the effect of sex, age, and cohort on network modularity. This analysis included an age-cohort interaction term to investigate modularity differences between typical and patient neurodevelopment.Results: No models

demonstrated a significant age-cohort interaction effect. Upon removing the interaction term, the maximum significant cohort effect was observed at a link density of 14% ($ß_{cohort}$ = -0.0323), coinciding with survivors' network modularity between 0.19 to 0.41. Within survivors, network modularity was not significantly related with intravenous nor intrathecal methotrexate dose. The variability in network modularity suggests the presence of unexplained survivor subtypes. Notably, survivors exhibited a lower prevalence of connections within the default mode, salience, and frontoparietal networks compared to controls. This discrepancy signifies underlying atypical functional connectivity that precedes neurocognitive late effects. Conclusions: Survivors of childhood ALL demonstrate atypical brain network modularity as early as the end of chemotherapy treatment. Further investigations into the clinical, therapeutic, and physiological mechanisms associated with this modularity are warranted.

Disclosures: J. Tanner: None. **W. Reddick:** None. **L. Jacola:** None. **K.R. Krull:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.17/C22

Topic: B.11. Neuro-Oncology

Support: R25 Bridge to the Doctorate Grant - 1R25GM107754
MCB 1955975 to S.R.

Title: Characterization and Function of Type II MAGEs in Normal Brain Physiology and Brain Tumorigenesis

Authors: *H. C. NNABUGWU, S. RAMANATHAN;
Biol., Fisk Univ., Nashville, TN

Abstract: Melanoma-associated Antigen (MAGE) proteins are the largest group of cancer-testis antigens (CTAs). They are further divided into Type I and Type II MAGEs based on expression pattern. While Type I MAGEs are true CTAs, Type II MAGEs are ubiquitously expressed in all tissues, with a notable higher expression in brain tissue. However, the role of Type II MAGEs in normal brain physiology and brain tumorigenesis remains unknown. In this study, we aim to understand the biochemical function of Type II MAGEs in normal brain tissue to explore their potential implications in brain cancer. We used the TCGA database and XENA browser to determine the expression profile of Type II MAGEs in normal brain tissue and compare it to brain cancer tissue samples. By comparing expression data between multiple cancer types, we were able to discover similarities in Type II MAGE expression. The biochemical function of some MAGE proteins is to bind to and enhance the activity of its cognate E3 Ubiquitin ligase binding partner. To determine the biochemical function of certain Type II MAGEs in the neuronal cells, we will use a combination of proteomics and genomics and gain and loss of function studies.

Disclosures: H.C. Nnabugwu: None. **S. Ramanathan:** None.

Poster

PSTR444: Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR444.18/C23

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

Title: Evaluation of IDH1, EGFR, IGF1R and Ki67 biomarkers in glioblastoma using Lunaphore COMET platform

Authors: *A. KALYUZHNY;
Antibody Validation, Bio-Techne, Minneapolis, MN

Abstract: Glioblastoma (GBM) is the most aggressive primary neuroepithelial tumor diagnosed in about 14,000 people in the United States each year. Patients with GBM have a poor prognosis and only 5% of these patients can survive for more than 5 years. Various biomarkers are used for Immunohistochemical (IHC) diagnosis of GBM including: Isocitrate dehydrogenase 1 (IDH1), Epidermal Growth Factor Receptor (EGFR), Insulin Like Growth Factor 1 Receptor (IGF1R), and a cell proliferating marker Ki67. Typically, IHC is done by using a single-biomarker HRP-DAB detection technique which is not suitable for the simultaneous spatial analysis of multiple biomarkers. In our previous study we developed a manual protocol for multiplex IHC for colocalization of above targets and the aim of this study was to employ automated ultra-rapid Lunaphore COMET platform which utilizes a multi-color immunofluorescence protocol allowing for the spatial biology analysis of distribution and co-localization of biomarkers across entire GBM tissue sections. Primary antibodies were: monoclonal mouse anti-human IDH1 (MAB7049), polyclonal goat anti-human EGFR (AF231), monoclonal mouse anti-human IGF1R (MAB391), and monoclonal rabbit anti Ki67 (MAB7617). For signal detection we used species specific secondary antibodies conjugated to fluorescent dyes with different excitation and emission spectra. As in our previous manual IHC staining protocol, we have observed high frequency of EGFR and IDH-1 co-localization whereas IGF-1R labeling was confined to a smaller number of cells. Immunoreactivity for Ki67 was the lowest and detected in about 5% of cells. Large number of EGFR-positive cancer cells were also immunoreactive for IDH-1 and IGF-1R. We observed that entire population of Ki67-labeled cells was also immunoreactive for EGFGR and IDH1R and only half of Ki67-positive cells were immunoreactive for IGF1R. The advantages of using Lunaphore COMET instrument include automatic removal of endogenous tissue autofluorescence, tissue-staining speed and high-resolution imaging allowing for rapid analysis of the spatial distribution of multiple GBM biomarkers and their co-localization at the single-cell level.

Disclosures: A. Kalyuzhny: None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.01/C25

Topic: C.01. Brain Wellness and Aging

Title: Decoding Delirium: Machine Learning Classification from Inpatient Wearable EEGs

Authors: *D. PRASAD[1], K. MAO[2], M. MENDU[3], H. SUN[4], B. F. COUGHLIN[5], A. LAM[5], S. S. CASH[6], M. B. WESTOVER[7], E. Y. KIMCHI[8];
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Abstract: Background: Delirium is an acute neuropsychiatric disorder of attention and awareness that significantly impacts hospitalized patients, particularly older patients, and is associated with increased dependence and death. Despite its prevalence, delirium detection remains challenging due to its fluctuating nature and the limitations of current clinical diagnostic tools. Using EEG data collected with a novel wearable sensor in hospitalized inpatients, we built a machine learning (ML) model to predict delirium.
Methods: We conducted a prospective observational study at a tertiary care academic medical center (n = 115) to develop and validate EEG-based machine learning models for delirium detection. Recordings were collected from a wearable EEG device. We extracted 2196 EEG features from single-channel EEG recordings. Skewed feature data was log-transformed. We conducted feature selection using chi-squared univariate, lasso regression, and minimum redundancy maximum relevancy (mrmr) approaches. We then fit four different supervised ML models (support vector machine (SVM), logistic regression, gradient boosting, and random forest) to predict delirium occurrence using fivefold cross-validation (80:20 train-test split). Feature generation was conducted in MATLAB R2022b and machine learning analysis was conducted with scikit-learn in Python 3.11.5.
Results: The model with the highest area under the receiver operating characteristic (AUROC) curve was an SVM model with 10 mrmr-selected features, demonstrating promising discriminative ability with an AUROC of 0.73, sensitivity of 65%, and specificity of 71%. Key features contributing to model performance included theta and delta band power metrics. The model performance surpassed the upper bound of a permutation test's null distribution, confirming its statistical significance over chance.
Conclusion: Our findings demonstrate that wearable EEG combined with automated feature extraction and machine learning modelling can effectively detect delirium. Ongoing work aims to refine feature selection, extend analysis to larger datasets, and develop models to go beyond categorical delirium status to predict continuous delirium severity in hospitalized patients.

Disclosures: D. Prasad: None. **K. Mao:** None. **M. Mendu:** None. **H. Sun:** None. **B.F. Coughlin:** None. **A. Lam:** None. **S.S. Cash:** None. **M.B. Westover:** None. **E.Y. Kimchi:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.02/C26

Topic: C.01. Brain Wellness and Aging

Title: Wearable EEG recordings show dysregulated sleep-wake patterns in hospitalized patients with delirium

Authors: *C. ZHAO[1], S. DHAR[1], I. SHERRINGTON[1], R. A. TESH[2], B. F. COUGHLIN[3], A. LAM[3], S. S. CASH[3], M. B. WESTOVER[2], E. Y. KIMCHI[1];
[1]Neurol., Northwestern Univ., Chicago, IL; [2]Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Background: Delirium is an acute state of confusion characterized by disturbances in attention and awareness, often accompanied by rapid fluctuations in cognitive function. Delirium affects >20% of hospitalized older adults and is frequently overlooked, despite being significantly associated with poorer clinical outcomes including death; >90% of patients with delirium experience disturbances in sleep-wake activity. However, the ways and mechanisms by which circadian rhythms are disrupted in delirium remain unclear.
Methods: Our cohort study analyzed 21 single-channel EEG recordings (24-hour durations) collected from 12 older patients (n =12; 8 non-delirious, 4 delirious) admitted to various inpatient wards at Northwestern Memorial Hospital. We defined delirium using the 3-minute diagnostic interview for the Confusion Assessment Method (3D-CAM) and compared sleep-wake patterns between delirious and non-delirious patients using both manual sleep staging (1-hour epochs) and the U-Sleep model (30-second epochs) for automated sleep staging to identify differences in sleep-wake patterns and sleep architecture among these two groups.
Results: Total duration of sleep obtained over a 24-hour period was not associated with delirium in both manual staging and U-Sleep methods (linear mixed effects model (LMEM) manual staging: $p = 0.118$; U-Sleep LMEM: $p = 0.133$). However, delirium did affect the consolidation and timing of sleep. Delirious patients exhibited a higher number of sleep-wake transitions compared to non-delirious patients when assessed using U-Sleep (rank-sum: $p = 0.018$). Additionally, the percentage of sleep occurring during typical hours differed significantly between delirious and non-delirious groups as observed in manual staging methods (LMEM: $p = 0.0015$). Non-delirious patients spent approximately 82% of their time asleep during normal sleep hours, while delirious patients only spent around 43% of their sleep time within this period (LMEM: $p < 0.001$). Additionally, the onset times of the longest periods of uninterrupted sleep varied significantly between the two groups (F-test: $p = 0.0028$).
Conclusions: In even a small, single-institution sample, sleep quality and structure, rather than quantity, were disorganized in patients with delirium. Ongoing work aims to extend analysis to a larger multi-institution cohort. Identifying specific circadian disruptions in sleep architecture may guide targeted interventions aimed at improving sleep onset and quality, potentially alleviating symptoms and improving outcomes in delirium patients.

Disclosures: C. Zhao: None. **S. Dhar:** None. **I. Sherrington:** None. **R.A. Tesh:** None. **B.F. Coughlin:** None. **A. Lam:** None. **S.S. Cash:** None. **M.B. Westover:** None. **E.Y. Kimchi:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.03/C27

Topic: C.01. Brain Wellness and Aging

Title: Using Video for Automated and Quantitative Delirium Assessment

Authors: *M. MENDU[1], E. JUAREZ MARTINEZ[2], R. A. TESH[4], K. PELLERIN[6], I. CERDA[8], S. SHAH[9], M. WILLIAMS[8], B. F. COUGHLIN[7], A. LAM[6], S. S. CASH[6], M. B. WESTOVER[5], E. Y. KIMCHI[3];
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Abstract: Delirium is an acute neuropsychiatric disorder that affects over 20% of older hospitalized patients. It remains underdiagnosed due to its dynamic and diverse manifestations. Current diagnostic methods are based on clinical evaluations that are subjective and intermittent. Since delirium is associated with heterogeneous psychomotor changes, we aimed to predict delirium status using video-based biomarkers. Patients hospitalized at a tertiary academic center underwent video recording during clinical delirium assessments. A human pose estimation model with a ResNet101 backbone was fine-tuned on 782 labeled frames to detect body points from patient videos using DeepLabCut. 283 facial and extremity movement related features were calculated from video data, respectively. Feature selection was performed using the chi-square test, minimum redundancy maximum relevancy (mRMR), and LASSO regression. Four machine learning models - logistic regression, gradient boosting, support vector machines, and random forests - were fitted with select behavioral features. Model performance was evaluated using 5-fold cross validation and area under the receiver operating characteristics curve (AUC). Out of 109 videos, 33 (30%) were of patients with delirium, respectively. The DLC pose estimation model had a median pixel-wise error of 3.65 and a sensitivity of 95.2% and specificity of 89.4% for point identification on the testing set, outperforming two off-the-shelf models. After multiple test correction, 22 video-based features were identified to be significantly different between patients with or without delirium. Patients with delirium had significantly decreased blink rates, pupil movements, and mouth movements. The gradient boosting model fitted on 10 video features selected via mRMR achieved the best performance for delirium classification with an AUC of 0.86, sensitivity of 80%, and specificity of 85.9% among the machine learning models. These results suggest the promise of video-EEG recordings for continuous delirium monitoring. Ongoing work aims to extend this approach to larger datasets.

Disclosures: M. Mendu: None. **E. Juarez Martinez:** None. **R.A. Tesh:** None. **K. Pellerin:** None. **I. Cerda:** None. **S. Shah:** None. **M. Williams:** None. **B.F. Coughlin:** None. **A. Lam:** None. **S.S. Cash:** None. **M.B. Westover:** None. **E.Y. Kimchi:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.04/C28

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

Support: NIH R01MH119165

Title: Epigenetic investigation of delirium: evidence replicated from four independent cohorts

Authors: *G. SHINOZAKI[1], Y. NISHIZAWA[2], T. YAMANASHI[3];
[1]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA; [2]Osaka Med. and Pharmaceut. Univ., Osaka, Japan; [3]Tottori Univ., Yonago, Japan

Abstract: Aims: Delirium, a clinical syndrome marked by sudden cognitive fluctuation, significantly complicates patient outcomes and increases morbidity. Detecting delirium, particularly post-operative delirium (POD), early in the clinical setting is crucial yet challenging due to the complex nature of its pathophysiology. Our study sought to identify stable and replicable epigenetic markers, specifically DNA methylation (DNAm) markers, that could serve as laboratory tools for delirium detection across various clinical settings. Methods: This study analyzed blood DNA from four independent cohorts—two from inpatient settings (Epigenetics of Delirium study: EOD1 and EOD2) and two from surgical settings (Neurosurgery: NSG and Tottori surgery: TSG), totaling 250 patients, using the Illumina EPIC array platform for comprehensive genome-wide DNAm profiling. We investigated the DNAm differences in patients diagnosed with delirium, including POD, against those without, to identify potential epigenetic biomarkers. Data collection methodologies, including participant recruitment at both the University of Iowa Hospitals and Clinics and Tottori University Hospital, were rigorously followed according to the respective ethical guidelines. Results: Our initial analysis identified 13 top CpG sites from the EOD1 cohort, which were then cross-analyzed with additional cohorts. 11 of these sites consistently demonstrated statistically significant DNAm differences in the same directions across the cohorts. The EOD1 and EOD2 cohorts showed similar DNAm level differences, with the majority of sites displaying lower methylation levels in delirium cases. Although pre-surgery samples from the NSG cohort showed no difference between groups, post-surgery samples again showed same results with 10 of 11 CpG sites confirming lower DNAm levels in POD cases, with nominal significance and comparable DNAm changes to other cohorts. The TSG cohort further validated these findings, showing significant DNAm differences at 8 sites, adjusted for age, gender, and cell counts. Conclusions: The consistent replication of DNAm changes across diverse clinical settings (surgery versus non surgery) and cohorts (non-Hispanic White from Midwest United States versus Japanese) underscores the robustness of these

epigenetic markers as potential diagnostic tools for delirium and POD. This study contributes significantly to our understanding of the epigenetic landscape of delirium, supporting the integration of DNAm biomarkers in clinical practice to enhance diagnostic accuracy and intervention strategies.

Disclosures: G. Shinozaki: A. Employment/Salary (full or part-time):; Stanford University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH, Sumitomo Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Predelix Medical LLC, Delight Health Inc. **Y. Nishizawa:** None. **T. Yamanashi:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.05/C29

Topic: C.01. Brain Wellness and Aging

Support: Alzheimer´s Association/National Academy of Neuropsychology Grant AAZ-NAN-22-941933

Title: Alterations in BNDF signaling in older adults with insomnia increases sigificantly in comparision to older adults with only cognitive decline

Authors: *N. A. RIVERO-SEGURA[1], P. GARCIA-DELATORRE[2], J. GOMEZ-VERJAN[3]; [1]Direccion de Investigacion, Inst. Nacional De Geriatría, Mexico City, Mexico; [2]UIM Enfermedades Neurológicas, IMSS-UIM Enfermedades Neurológicas, Cuauhtémoc, Mexico; [3]Res. Dictatoriate, Natl. Inst. of Geriatrics (INGER), Mexico City, Mexico

Abstract: The Brain-derived Neurotrophic Factor (BDNF) plays a key role in the central nervous system through the interaction of BDNF and its high-affinity receptor TrkB, a tyrosine kinase receptor, that triggers the activation of many biological activities such as with neural survival, synaptic plasticity and neurotransmission regulation. Nevertheless, BDNF concentration is dynamic and it can be affected by several stimuli such as lifestyle, stress, brain injury, psychiatric diseases, sleep or age. In this sense, it has been reported that older adults have lower levels of BDNF in comparison to young adults, and this observation has led to suggest BDNF as a potential biomarker for health during aging. However, to our knowledge, little is known about the potential stressors that during aging are more likely to affect both BDNF levels and signaling. In this sense, our research group has been focused on studying the effect of insomnia, the most common sleep disorder occurring during aging, on the BDNF signaling, including both BDNF concentration and the expression of TrkB. In the current study we quantify the BDNF concentration on serum samples of Mexican older adults with insomnia or cognitive

decline, and then we performed multivariate analysis to associated the BDNF concentrations with the main clinical, demographic and socioeconomic variables to identify the contribution of other factor on BDNF concentration. Our results demonstrate that insomnia significantly decreases the BDNF concentration as compared to the concentration measured in older adults with only cognitive decline. Interestingly, such association analysis shows that insomnia is significantly associated with lower levels of BDNF, suggesting that insomnia is more likely to decrease BDNF concentration in older adults in comparison with individuals with only cognitive decline.

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Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.06/C30

Topic: C.01. Brain Wellness and Aging

Support: Project-ID: 425899996 – SFB 1436, Deutsche Forschungsgemeinschaft (DFG)
Alzheimer Doctoral Scholarship from theHans und Ilse Breuer-Stiftung

Title: Medial septum integrity as a predictor of human path integration performance

Authors: *P. BAHRD, V. SEGEN, T. BELGE, T. WOLBERS;
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Abstract: Path integration is the ability to keep track of one's position while moving, by integrating internal and external self-motion cues. This ability is important for successful navigation and declines in both normal and pathological ageing, possibly due to age-related disruptions of grid cell dynamics in the entorhinal cortex. Critically, grid cells receive GABAergic input from the medial septum, the silencing of which disrupts grid cell firings in rodents. As a consequence, an intact medial septum in old age could help preserve path integration abilities. To test this hypothesis, we recruited healthy older adults (n=62) aged 60-95 years (M=76.2, SD=8.4, 26 females). To maximise ecological validity of the path integration assessment, participants walked along curved paths in a fully immersive virtual environment - providing them with both body-based and visual self-motion cues - along which they were asked to indicate from where they started. Path integration performance was quantified as the euclidean distance between true and estimated start location. To assess one aspect of medial septum integrity, we extracted total medial septum volume from structural T1- weighted MRI images at 3T, using previously defined subregional basal forebrain masks. In a multiple linear regression, we found no main effect of volume, age or sex. However, we found an interaction effect between medial septum volume and by age, such that higher age and lower volume leads to higher path

integration error. Further, we found that women benefit more than men from larger medial septum volumes. Together, our results suggest that maintenance of the medial septum integrity, via preserved volume, could be important for preserved navigation abilities in old age and in women, respectively. As GABAergic modulation deteriorates with age, it is plausible that preserved medial septum volume becomes a critical factor in later stages of ageing for sustainment of cognitive functions. Additionally, females undergo steeper GABAergic changes, possibly explaining their benefit of a larger medial septum. However, since only about a quarter of the neuronal population in the medial septum are GABAergic, potential atrophy of these neurons might not be fully captured by volumetric estimations alone. Thus, future work will look more directly into changes in GABAergic modulation in old age.

Disclosures: P. Bahrd: None. **V. Segen:** None. **T. Belge:** None. **T. Wolbers:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR445.07/C31

Topic: C.01. Brain Wellness and Aging

Support: CIHR - Canada Graduate Scholarship-Master's

Title: Uncovering the imaging and extracellular vesicular signature of mild cognitive impairment

Authors: *J.-L. WU[1], S. BERBERIAN[2], J. RAMIREZ[2], J. D. EDWARDS[3], S. N. WHITEHEAD[1];
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Abstract: Mild cognitive impairment (MCI) is a prevalent condition and often regarded as the prodromal stage to Alzheimer's Disease and other forms of dementia, making early diagnosis crucial for interventions and therapeutics. White matter hyperintensities (WMH) and enlarged perivascular spaces (EPVS) are magnetic resonance imaging (MRI) markers associated with MCI; however, these structural MRI markers have low sensitivity for early detection of cognitive decline. Extracellular vesicles (EVs) released by cells are an alternative candidate biomarker, as they can pass through the blood-brain barrier into peripheral circulation and possess surface markers and cargo reflecting the cell's physiological state. Therefore, we propose that combining both EV and MRI features as complementary biomarkers could improve their sensitivity and diagnostic utility for the detection of MCI. In this study, we aimed to quantify WMH and EPVS burden, correlate them with circulating EV markers, and determine whether these biomarkers together can discriminate cognitive status. A nested cohort of participants was selected from the Gait and Brain Cohort Study (NCT03020381), grouped into patients with MCI (n=40) or cognitively normal (n=40), balanced for sex and age. Patient MRI scans were analyzed using a

semi-automated pipeline to quantify WMH and EPVS volumes. Microglia and astrocyte EVs were measured with various combinations of EV surface markers and cargo in patient blood plasma samples. Early results showed that patients with MCI had increased WMH burden, decreased number of TMEM119+ EVs (a microglia marker), and increased proportion of TMEM119+/pTau181+ EVs, suggesting that phagocytosed pTau181 in microglia may be an indicator of MCI. Linear regression showed that TMEM119+/pTau181+ EVs were positively correlated with WMH burden, indicating that microglial clearance of pathological proteins may play a role in the etiology of WMHs. Preliminary discriminant analyses showed that discriminant models trained using both MRI and EV measures to discriminate MCI have greater accuracy, sensitivity, and area under the curve than models trained using either marker type alone, demonstrating the potential diagnostic utility of MRI and EV markers together. Further experiments will expand upon this to look at EVs of other microglia and astrocyte phenotypes. This study is the first to correlate WMH and EPVS with circulating brain EVs, as well as the first to explore their combined potential for discriminating cognitive status. This work will improve our understanding of the etiology behind WMH and EPVS and set the groundwork for novel biomarker development for MCI diagnosis.

Disclosures: J. Wu: None. **S. Berberian:** None. **J. Ramirez:** None. **J.D. Edwards:** None. **S.N. Whitehead:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.08/C32

Topic: C.01. Brain Wellness and Aging

Support: Psychiatry in Southern Region of Denmark, Mental Service Hospital
Independent Research fund, Southern Region of Denmark
Alzheimer Foundation Denmark

Title: Unravelling the neurobiology of healthy aging: The crucial role of insula

Authors: *M. SEYEDI VAFAEE[1,2], L. KNUDSEN[1], T. MICHEL[3];
[1]Univ. of Southern Denmark, Odense, Denmark; [2]Psychiatry Research Unit, Odense, Denmark; [3]Psychiatry Res. Unit, Odense, Denmark

Abstract: Purpose: Understanding the neurobiology of healthy aging is paramount for enhancing quality of life and preventing age-related diseases. Our objective was to leverage advanced neuroimaging techniques to shed light on neurophysiological parameters, particularly the interplay between cerebral glucose metabolism and Aß plaques deposition throughout the lifespan. By doing so, we aimed to unravel the intricate processes that underlie cognitive and neural health. **Methods:** Eighty healthy subjects between 20-80 years underwent one ^{11}C-PiB and one ^{18}F-FDG PET scans and a series of simultaneous MRI scans including arterial spin

labeling (ASL) and diffusion tensor imaging (DTI) scans for the measurement of cerebral blood flow (CBF) and white matter integrity (WMI) accordingly.**Results:** Our study showed a positive correlation between advancing of age and the accumulation of Aß plaques in the whole brain, with particular prominence observed in the regions such as hippocampus, posterior cingulate gyrus and orbitofrontal cortex. Furthermore, global cerebral glucose metabolism as an index of neuronal activity revealed a robust negative correlation between age, white matter (WM) and grey matter (GM) density in similar regions as Aß deposition occurred, hinting that increases in Aß plaques have detrimental effects on metabolism, GM and WM integrity. Interestingly, despite the global decline in cerebral glucose metabolism observed, there were intriguing regional increases detected in certain temporal and frontal areas. Notably, the insula exhibited the most pronounced elevation in glucose metabolism.**Conclusion:** Our findings suggest that while the deposition of Aß plaques leads to the deterioration of glucose metabolism in various brain regions, there are also areas, such as the insula, where metabolism increases compensatorily. This counterbalancing mechanism appears to mitigate the adverse effects of Aß plaques, thereby preserving brain health and hindering the progression towards neurodegeneration.

Disclosures: M. Seyedi Vafaee: None. **L. Knudsen:** None. **T. Michel:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.09/C33

Topic: C.01. Brain Wellness and Aging

Support: NSF GRFP Grant# 2036201

Title: The effect of aging on reaching velocity in a motor adaptation paradigm with temporal delays

Authors: *J. KORTE[1], F. DOGBE[2], W. M. JOINER[2];
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Abstract: Normal aging is associated with a decline in learning, memory, and movement speed, all of which are components that affect overall motor performance. This study sought to investigate how cognitive changes with age are reflected in these distinct mechanisms. Specifically, we examined the impact of temporal delays on implicit and explicit processes, and their relationship to movement speed. Motor adaptation studies are a tractable method to assess different components of learning and memory, and previous work has demonstrated implicit and explicit learning contributions to motor adaptation during a visuomotor rotation (VMR) task. This task measures motor planning and adaptation by inducing a rotational offset (e.g., 45^{o}) to visual feedback as the participant moves a cursor on a screen with an arm reaching movement. Explicit learning is quantified by the intended direction the subject selects prior to each

movement, while implicit learning is derived from the difference between this selected movement and the actual hand movement. This task has been used to examine adaptation savings (faster relearning when the perturbation is experienced again following a break) and temporal stability (the retention of learning assessed by evaluating the amount of learning over a short delay period, e.g., 10 to 90 seconds). To investigate the extent delay affects reaching velocity, we compared peak velocity, movement duration, and velocity profiles during adaptation across healthy young (18-25; N=22; 15 female) and older (60-85; N=22; 14 female) cohorts following short delay periods. We also examined the relationship between vigor metrics and implicit and explicit performance. The velocity of younger subjects' reaching movements were significantly correlated with delay times (the amount of time waiting prior to making their reaching movement; $p<0.05$) and with the decay of implicit learning performance ($p<0.05$). Older participants demonstrated consistently reduced velocity after delays, but we found no correlation between implicit decay nor with delay times. These results indicate that with advanced age, time delays will result in reduced movement velocity, regardless of the delay duration. Movement kinematics did not correlate with implicit decay, indicating that movement velocity is separate from learning processes, but may be reflective of cognitive processing prior to reaching movement.

Disclosures: J. Korte: None. **F. Dogbe:** None. **W.M. Joiner:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR445.10/C34

Topic: C.01. Brain Wellness and Aging

Support: HBP SGA2
HBP SGA3
ER 155/6-1
ER 155/6-2
SI 236/8-1
SI 236/9-1

Title: Linking individual variability in multi-modal connectivity, lifestyles, and cognition in older adults

Authors: *M. ZHANG[1,2], N. BITTNER[1,2], S. CASPERS[1,2];
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Abstract: Older adults exhibit greater heterogeneity than younger adults, not only in behavior and cognition but also in brain. This may be influenced by genetic and environmental factors over the lifecourse, including lifestyle. While it has been shown that individual variability (IV) of

functional (IV_{FC}) and structural connectivity (IV_{SC}), which assess brain heterogeneity, are correlated with age, further empirical evidence is needed to understand the factors contributing to this heterogeneity among older adults. We reconstructed the functional and structural connectivity of 421 cortical, subcortical, and cerebellar regions in 461 participants (mean age = 67.25 years) from the population-based 1000BRAINS study[1]. We calculated the brain connectivity IV according to a previous study[2]. Our aim was to explore the relationship between region-wise brain connectivity IV, lifestyles, and cognitive function. We, therefore, used partial least squares correlation (PLSC), controlling age, gender, and education as covariates. Additionally, we were interested in the specific patterns within the older adult lifespan and thus performed the same analyses for three age subgroups (55-65 65-75, and > 75 years) separately. We observed a significant latent variable (LV) explaining 40.06% of the shared variance among all included variables. This LV linked higher connectivity IV with lower cognitive performance, especially executive control, as well as an unhealthy lifestyle pattern (Spearman $r = .307$, $p < .001$), characterized by higher packyears of smoking and less social integration. The IV_{SC}, particularly of parts of the right middle frontal, precentral, left middle temporal, and cingulate gyrus, contributed more to this relation pattern than the IV_{FC}. Additionally, we observed varying patterns of association between connectivity IV, lifestyles, and cognition across different age subgroups. While the 55-65 and 65-75 groups exhibited similar patterns to the whole group, alcohol consumption and cognitive function specifically were negatively associated with brain connectivity IV in the 75-85 years group. This study links brain heterogeneity to lifestyle and cognitive factors, suggesting that higher connectivity IV is associated with unhealthier lifestyles and lower cognitive performance with the pattern of this relationship varying by age group. IV_{SC} tends to have a greater contribution than IV_{FC} to this relationship. These findings highlight how lifestyle introduces heterogeneity in brain connectivity among older adults. [1] Caspers, S., et al. (2014). Frontiers in Aging Neuroscience, 6(JUL). [2] Mueller, S., et al. (2013). Neuron, 77(3), 586.

Disclosures: M. Zhang: None. **N. Bittner:** None. **S. Caspers:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR445.11/C35

Topic: C.01. Brain Wellness and Aging

Support: Quebec Bio-Imaging Network (QBIN)
Long COVID Web (LCW)
Consejo Nacional de Ciencia y Tecnologia (CONACyT)
Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR)

Title: Unraveling Altered Brain Function in Post COVID-19 Condition Through Electroencephalography

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Abstract: Even though COVID-19 is primarily a respiratory illness, it can affect more than 10 physiological systems, with over 200 reported symptoms. Around 30% of individuals infected with COVID-19 experience symptoms persisting beyond 12 weeks post-infection, known as Post COVID-19 condition (PCC). The 3 main symptoms of PCC 6 months post-infection include fatigue, brain fog, and post-exertional malaise. PCC has been associated with changes in the blood-brain barrier, grey matter loss, and decreased brain excitability. These brain changes may underlie the residual and persisting symptomatology of PCC. This study aimed to identify the electrophysiological correlates associated with the main lingering symptoms of PCC. We used electroencephalography (EEG) data captured with a 64-channel cap (Brain Products, Germany) to explore the changes in brain oscillatory and functional properties during rest and hand movements in 20 PCC participants (43±10 yo; 14 females; 24±11 months post-infection) and age- and sex-matched controls. Mean post-movement beta rebound (PMBR), measured as percent change in beta power relative to baseline, was found to be significantly lower in the PCC group (2.4% ± 17.4%) over the sensorimotor area (at electrode C3, p=0.037) compared to the control group (20.1% ± 25.6%), as determined by an independent samples t-test. Additionally, the aperiodic exponent of the power spectral density measured at rest was significantly elevated in PCC within slow frequencies (2-7 Hz), specifically at the parietal lobe electrodes Pz (p=0.009) and CPz (p=0.002). The mean values for Pz were PCC=.98 ± .5 and controls=.38 ± .36, and for CPz, PCC=.93 ± .53 and Control=.34 ± .3), also determined by independent sample t-tests. Pearson correlation analyses showed that higher aperiodic exponents were associated with fatigue severity scale (FSS) (r=.49, p=0.005) and cognitive failures questionnaire (CFQ) scores (r=.45, p=0.01) at CPz, and with FSS (r=.45, p=.01) and CFQ (r=.36, p=.04) at Pz. Reduced PMBRs observed in PCC suggest impaired sensorimotor control, affecting motor inhibition and learning. Elevated aperiodic exponents over the parietal and central regions suggest increased neuronal inhibition in sensory and motor processing areas. The associations between specific EEG features and clinical scores underscore their value as potential biomarkers for the symptomatology present in PCC. These results represent a critical step toward developing diagnostic methods and targeted treatments to alleviate the debilitating symptoms experienced by this population.

Disclosures: M. Casado Sanchez: None. **C. Duclos:** None. **M. Boudrias:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.12/C36

Topic: C.01. Brain Wellness and Aging

Support: DBT/Wellcome Trust India Alliance (Senior fellowship IA/S/18/2/504003) to SR
Axis Bank PhD fellowship to AB
Prime Minister's Research Fellows to SA

Title: Enhanced stimulus-induced and stimulus-free gamma in open-eye meditators

Authors: *A. BISWAS[1], S. AGGARWAL[2], K. SHARMA[3], S. RAY[4];
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Abstract: Gamma oscillations (~30-80 Hz) are known to be modulated by high-level cognitive processes such as attention, memory, and meditation and, therefore, could provide clues about mechanisms underlying high-level cognition. Interestingly, gamma oscillations can be "induced" in the brain by presenting certain stimuli such as bars, gratings, and color patches (especially red hues). Moreover, these stimulus-induced gamma oscillations decrease with age and are abnormal in patients with several brain disorders like Alzheimer's Disease and Schizophrenia. While previous meditation studies have observed changes in endogenous (stimulus-free) gamma with meditation, no study to date has tested if stimulus-induced gamma oscillations are also modulated by meditation. We collected EEG data from 35 long-term meditators from the Brahmakumaris tradition who practice meditation with open eyes, and 36 age- and gender-matched controls. We presented full-screen achromatic stimuli that induce gamma before, during and after meditation. These stimuli induced two gamma waves, called slow (24-34 Hz) and fast (40-70 Hz), which have been associated with the somatostatin and parvalbumin positive inter-neuronal networks, respectively. We found that stimulus-induced gamma, like stimulus-free gamma, was stronger in meditators, but specifically in the slow gamma range. Interestingly, both gamma signatures co-existed during meditation but were unrelated and prominent in occipital and fronto-temporal regions, respectively. Further, we found that the power spectral density (PSD) slope, which becomes shallower with aging, was steeper for meditators. Together, our results indicate that meditation could boost inhibitory mechanisms leading to stronger gamma and steeper PSDs, potentially providing protection against aging and neurodegeneration.

Disclosures: A. Biswas: None. **S. Aggarwal:** None. **K. Sharma:** None. **S. Ray:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.13/C37

Topic: C.01. Brain Wellness and Aging

Support: Sylvan Adams Sports Science Institute
Canadian Institutes of Health Research
Fonds de Recherche du Quebec - Sante

Title: Long-term, high-level aerobic training and the age-related decline in cortical thickness

Authors: *S. PERFETTO[1,3], A. POTVIN-DESROCHERS[4], I. SIERRA[1,3], C. MVOMO[1,3], J. SHOEMAKER[5], M. M. CHAKRAVARTY[2], C. PAQUETTE[1,3];
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Abstract: The cerebral cortex naturally thins as humans age. Declines in cortical thickness are associated with poorer cognitive performance and an increased susceptibility of both falls and Alzheimer's disease. Regular aerobic exercisers, such as masters athletes, have displayed thicker cortices relative to less active age-matched adults. However, the cortical thickness of older long-term exercisers has not been compared to that of younger regular exercisers, limiting the understanding of how regular aerobic training influences cortical thickness at different age points. The objective of this study was to quantify and compare differences in cortical thickness between high-level athletes and healthy controls at both young and older ages. This study retrospectively compared cortical thickness in 27 young athletes (mean age = 28±4), 27 young controls (age = 24±2), 15 older athletes (age = 78±7), and 18 older controls (age = 75±9). T1-weighted magnetic resonance imaging (MRI) scans were acquired with a Siemens 3T Prisma or a Trio Scanner [echo time = 7.10ms (Trio), 2.96-2.98ms (Prisma); repetition time = 2,300ms, flip angle = 9°, 192 slices, voxel size = 1mm^3 isotropic]. Cortical thickness estimates were derived from the T1-weighted images using a series of established steps in CIVET 2.1.1 and were analyzed using the SurfStat toolbox and SPSS 29.0.0.0. The Kruskal-Wallis and Dunn's Tests revealed no significant difference in mean global cortical thickness between young controls (3.04±0.09 mm) and young athletes (3.02±0.07 mm, p = .470), as well as between older controls (2.72±0.17 mm) and older athletes (2.73±0.13 mm, p = .914). The variability of cortical thickness was assessed with the Brown-Forsythe and Mann-Whitney U tests. In controls, cortical thickness variability significantly increased from young to older age (young: 0.009 mm vs. old: 0.030 mm, U = 174.00, z = -2.22, p = .026), while there was no significant increase observed in the athletes (young = 0.005 mm vs. old = 0.017 mm, U = 166.50, z = -0.95, p = .345). The variability of cortical thickness remains lower in older age in an athletic population in comparison to controls. These results suggest that control older adults have regions of increased or decreased cortical thickness, while these differences may not be seen in older athletes. This finding highlights that older athletes may be less susceptible to age-related alterations in cortical thickness.

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Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.14/C38

Topic: C.01. Brain Wellness and Aging

Support: European Union's Horizon 2020 Research and Innovation Program under Grant Agreement No. 785907 (HBP SGA2; SC)
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German Research Council ER 155/6-1
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Title: Impact of methodological choices when reconstruction specific streamline fiber tracts

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Abstract: Using diffusion weighted imaging to study specific fiber tracts allows for various reconstruction options. Selecting tracts from a previously built whole brain connectome with a fixed streamline number seems to be recommended. The biological validity of such method for all participants, with different age or disease status and, thus, structural decline, remains unclear, pointing to other methods, such as directly sampling streamlines for a given tract. We tested systematically, whether different tract reconstructions led to the same biological outcomes, here represented by age effects of the Corpus Callosum (CC). After preprocessing diffusion-weighted data from the population-based 1000BRAINS cohort (n = 1009 participants, 553 females, 18 - 85 years), we compared different reconstructions of the tracts of interest, i.e. seven subregions of the CC, using probabilistic anatomically constrained tractography: 1. We selected streamlines from a whole brain tractogram with a fixed number of 10 Mio streamlines. 2. We directly selected streamlines randomly seeded in each voxel of the CC´s mid-sagittal (1000 versus 500 seeds per voxel). Streamline count versus sift2 were used to examine age-related differences regarding percentage of explained variance (%) by age for best fitting quadratic regressions. Comparing the two methods revealed slightly different patterns depending on the selection approach: When selecting tracts from a whole-brain tractogram (1), pronounced age-related differences were found across the whole CC with focus on anterior to middle CC for streamline count and sift2 (up to 27.1%). When seeding from the mid-sagittal (2), this focus in the anterior to middle CC was preserved, but much less pronounced (up to 5.4 %), while no age effects in posterior CC were observed for streamline count. While sift2 also showed the strongest effects in the anterior CC subregions (15.3 %), all CC subregions presented age-related decline (> 2.5%). Depending on the reconstruction setup, biological age effects are reflected differently. Selecting specific streamlines from a whole brain tractogram presented more pronounced age effects than directly selecting from a region of interest. This might hint at an overestimation, when selecting from a whole tractogram, possibly reflecting shifts of streamline reconstruction (to reach the total

defined number) rather than decline. Yet, when seeding specific streamlines, counts might underestimate age effects in comparison to sift2 weights, presenting a balanced pattern between both methods. However, most reconstruction setups replicated age-related differences in anterior CC regions in line with literature.

Disclosures: N. Bittner: None. **P.R. Dellani:** None. **S. Caspers:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.15/C39

Topic: C.01. Brain Wellness and Aging

Support: Alzheimer's Disease Research Center grant from the National Institute of Aging (P30AG072977)
SuperAging R01 from the National Institute on Aging (R01AG067781)
SuperAging U19 from the National Institute on Aging (U19AG073153)

Title: Higher Pre and Postsynaptic Proteins in Cognitive SuperAgers Compared with Cognitively Average Controls

Authors: *R. D. TAEFI[1], T. HILL[2], I. A. AYALA[3], K. HAYNES[4], R. J. CASTELLANI[5], P. JAMSHIDI[2], E. J. ROGALSKI[6], T. GEFEN[7], M.-M. MESULAM[8], C. GEULA[9];
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Abstract: Although memory decline is a typical characteristic of the aging process, the Northwestern SuperAging Research Program has identified individuals who display superior memory performance in old age. "SuperAgers" (SA) are over age 80 and perform on tests of episodic memory at least equivalent to those 20-30 years younger. Initial studies showed that on average SAs have larger cortical volumes, more von Economo neurons, and less prevalence of Alzheimer's disease (AD) pathology compared to their cognitively average peers. Synaptic loss strongly correlates with cognitive decline, particularly in individuals with AD. The purpose of this study was to investigate whether the SuperAging phenotype is associated with greater synaptic integrity. We examined levels of the presynaptic protein synaptophysin and the postsynaptic density protein 95 (PSD-95) in fresh frozen tissue of six brain regions, including middle frontal gyrus (MFG), superior temporal gyrus (STG), middle temporal gyrus (MTG),

hippocampus (HPC), primary visual cortex (VIS), and cerebellum (CER). We also analyzed levels of spinophilin, a dendritic spine protein which forms the postsynaptic element of most synapses in the CNS. We analyzed these three synaptic proteins in SuperAgers ($N \geq 11$) and cognitively average elderly ($N \geq 8$) using Western blot analysis. Optical densities of Western blot bands for synaptic proteins were expressed as a percentage of the GAPDH housekeeping protein. Levels of synaptophysin were significantly higher in MTG ($p = 0.04$) in SuperAgers when compared with cognitively average controls. PSD-95 showed a general trend of higher levels in SuperAgers in MFG, STG, and CER regions (11-14% increase). Spinophilin levels displayed a consistent increase in SuperAgers in all regions examined, which approached significance in STG ($p=0.09$), HPC ($p=0.09$), and VIS ($p=0.08$). These findings suggest that enhanced integrity of cortical synapses may contribute to the SuperAging phenotype.

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Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.16/C40

Topic: C.01. Brain Wellness and Aging

Support: CRC-2018-00042
CIHR STEFANOVIC,B-CIHR PJT156179 1018245 410009513
CIHR STEFANOVIC,B-CIHR PJT173409 1022274 410013821
CIHR STEFANOVIC,B-CIHR PJT191806 1028209 410020048

Title: Deep brain phenotyping of time-dependent response variability in BOLD fMRI

Authors: *E. PINEAU[1], K. CHEN[2], A. TREVISIOL[2], M. KOLETAR[2], M. BELL VILA[1], M. GOUBRAN[1,2], J. G. SLED[1,3], B. STEFANOVIC[1,2];
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Abstract: Healthy brain function involves *continual* remodeling of the functional properties of the neurons - even under environmentally and behaviourally *stable* conditions. The brain undergoes ongoing, activity-independent synaptic remodeling, leading to time-dependent variation in the individual neuron's membrane hyperpolarization and thereby stochasticity in its responsiveness to stimuli. On a population level, we hypothesize that an ever-shifting subset of neurons is activated on repeated stimulation trials, creating variability in brain-wide activation patterns. Assays quantifying variability in neuronal activity have been reported, leveraging *in vitro* models and techniques that provide single-cell resolution; however, reliable estimations of variance on a whole-brain, system level have not been done to date.In this exploratory research

study, we have undertaken blood oxygenation level dependent (BOLD) functional MRI (fMRI) to investigate similarity in activation patterns across repetitive transcutaneous electrical stimulation of the forepaw (5 mA, 333 μ;s pulses delivered at 3-Hz, 60-s ON/ 240-s OFF blocks, with 27 stimulation trials) in 22 (13-female/9-male) dexmedetomidine-sedated (subcutaneous delivery: 50μ;g/kg bolus, maintained by 100 μ;g/kg/hr continuous rate infusion) aged (12-15 months old) Fischer 344 rats that were also cognitively and electrophysiologically characterized. The fMRI was undertaken on our 7T Bruker MRI (TE/TR 30-ms/2000-ms, FOV 1.92x1.92-cm, 64x64 matrix) in ten 2-mm thick slices, 0.2-mm apart. To understand how neuronal engagement volatility may manifest on fMRI activation maps, we contrasted baseline vs. activation signal intensity profiles, estimated by the generalized linear model analysis. Contrary to conventional notions of functional specialization of brain areas, this simple sensory stimuli evoked very broad activations across the brain that could be detected due to the higher than usual fidelity of our extended (3-hour long) imaging protocol. Our results indicate significant across-trial intra-subject fMRI response variability and notable inter-individual differences in the amount of within-subject variability in across-trial fMRI responses. The deep within subject characterization during this long acquisition protocol, in combination with cognitive and electrophysiological data in the same subjects, is expected to provide new insights into the sources of variability in traditional BOLD fMRI experiments, and the cognitive salience of this variability.

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Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.17/C41

Topic: C.01. Brain Wellness and Aging

Support: Kempe Foundation,Örnsköldsvik, Sweden (Grant JCK-1922.2)
The Strategic Research Area Neuroscience (StratNeuro), Umeå University, Umeå Sweden

Title: Streamline tractography of the mouse corpus callosum: uncovering topographical order across the animal's lifespan and white matter changes during aging

Authors: *F. SULTAN[1], T. MEDIAVILLA[2];
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Abstract: Detection of white matter integrity plays an important role in studying the pathology of neurodegeneration in the aging brain. The corpus callosum (CC) is the major tract connecting the two cerebral hemispheres and is important to study white matter changes during aging. Diffusion-weighted MRI is an excellent tool to study the mesoscopic organization of human

white matter. Here we applied DW-MRI tractography to longitudinally study the fiber organization of the mouse CC across most of its lifetime (middle to old: 6 to 24 months). Our results reveal the projection sites of different cortical areas in the CC. These areas include frontal, motor, and sensory areas as well as cingulate and parietal regions. Furthermore, the mouse CC organization confirms the human spatial order with frontal regions occupying the rostrum and parietal-visual the posterior splenic region. The primary somatosensory cortex also shows a somatotopic organization. Our analysis also reveals age related changes in fiber density of the anterior cingulate, retrosplenial area, primary somatosensory and motor cortex.
In summary, we confirm a mammalian-like organization with most regions showing an ordered spatial organization and sharing their CC territories with more than one area. Our analysis also reveals important connections that changes in fiber density during aging.

Disclosures: F. Sultan: None. **T. Mediavilla:** None.

Poster

PSTR445: Assessing Brain Wellness in Humans and Animal Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR445.18/C42

Topic: C.01. Brain Wellness and Aging

Support: NIH R21OD023838 (KJM and BRN)
NIH R21OD030107 (KJM)
Impetus Longevity Award (BRN)

Title: Spiny Mice maintain hippocampal stem cell niche activity during aging and after injury

Authors: *G. MULLINS[1], J. HONG[1], B. R. NELSON[1], K. J. MILLEN[2];
[1]Seattle Children's Res. Inst., Seattle, WA; [2]Pediatrics, Seattle Children's Res. Inst., Seattle, WA

Abstract: Age-related neurodegenerative disorders and dementias like Alzheimer's Disease are an increasing medical, familial, and economic burden. The hippocampus and neural stem cell (NSC) niche within the dentate gyrus (DG) are sensitive to acute and chronic systemic inflammatory signals that normally promote gliosis, quiescence, and suppress neurogenesis in mammals. The hippocampus is also a key Alzheimer's Disease initiating site, hence serving as a general gauge for overall brain health span. Acomys cahirinus, "Spiny Mice," are rodents with novel regenerative and resiliency adaptations contributing to better healthspans and longer lifespans compared to standard mouse (Mus musculus) models. Initial comparative studies indicated relatively higher levels of adult DG neurogenesis in Acomys compared to other mammals, which also decreases during aging. Yet, critical information about progenitor levels and subtype identities coupled with niche activity, output, dynamics, location, and resiliency are not known. Here, we confirm Acomys increased general DG progenitor proliferation, which we show further occurs through expanded NSC and intermediate progenitor pools indicated by key transcription factor neurogenic markers. 2X-thymidine analog labeling reveals highly dynamic

DG niche proliferative activity, often localized in large progenitor clusters throughout the entire DG niche. We tested Acomys DG niche activity and output during aging using 2X-thymidine analog labeling, which revealed Acomys aged DG niche proliferative activity remains the same as Acomys young DG niche activity, and despite a general decrease in aged DG niche neurogenic output, aged Acomys continue to generate a relatively large number of new neurons throughout their longer lifespan. Acomys also exhibit increased survivability to high-dose LPS systemic inflammatory injury compared to Mus, and Acomys survivors recover DG niche proliferative activity and regenerate neurogenic output. Hence, Acomys persistent proliferation provides continuous hippocampal stem cell niche activity during aging and promotes neurogenic regeneration after systemic inflammatory injury, key brain health span and longevity traits that have important implications for understanding better human brain aging.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.01/C43

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

Title: Alcohol Use Disorder Augments Alzheimer's Disease and Dementia: Implication of Post-synaptic Modification

Authors: *Y. XU;
Rutgers Univ., Newark, NJ

Abstract: Background: Chronic alcohol use disorder (AUD) is widely acknowledged as a significant risk factor in the advancement of Alzheimer's disease (AD). The intricate interplay between alterations in inflammatory response and infiltration of immune cells closely links with the onset and progression of dementia associated with both AUD and AD. **Methods:** APP/PS1 mice underwent intermittent ethanol treatment via intraperitoneal injection (EtOH, 2.5 g/kg, i.p.) for ten weeks, with two "drug-free" days every 5 days. Brain tissues were harvested for RNA-sequence and molecular biological pathway analyses, subsequently validated using real-time RT-PCR and ELISA assays. **Results:** The analysis revealed 1675 up-regulated genes in the APP/PS1 group compared to WT littermates, exhibiting correlation with Rbm15b target genes. Additionally, 300 up-regulated genes demonstrated alterations in ethanol-treated AD mice as compared to age-matched AD mice, also correlated with Rbm15b. These genes predominantly participated in neurodegenerative processes and GABAergic synapses, as evidenced by KEGG and GO analyses. Moreover, they were implicated in pathways associated with glutamatergic synapses, calcium metabolism, cAMP signaling, and postsynaptic modifications. The findings from RNA sequence analysis were corroborated through subsequent real-time RT-PCR and ELISA assays. **Conclusions**: The study suggests a correlation between chronic ethanol

consumption and post-synaptic modulation in the progression of Alzheimer's disease, potentially mediated through postsynaptic modifications and alterations in inflammatory response.

Disclosures: Y. Xu: None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.02/C44

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

Title: Expression of Alzheimer's genes alters movement characteristics of the fruit fly, Drosophila melanogaster

Authors: A. B. COOK[1], J. M. SCIANDRA[1], A. L. DRAPER[1], A. D. CASTILLO[2], R. M. MELLETT[2], F. LIN[2], *R. M. YODER[1];
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Abstract: The expression of Alzheimer's genes in drosophila contributes to the aggregation of amyloid *β-42 (*Aβ42*)*, a shortened lifespan, impaired climbing abilities, and altered movements in several behavioral tasks. However, we currently have limited evidence to indicate whether these deficits are reversible or otherwise treatable. Here, we crossed an *Elav^{c155}Gal4* strain to a *UAS-Aβ42^{arc}* line (*Drosophila* Stock Center, Bloomington, IN) to produce *Aβ42^{arc}*-expressing (Alzheimer's) flies. It has been shown that amyloid protein aggregates in the Elav-*UAS-Aβ42^{arc}* flies are correlated with locomotor dysfunction. The Alzheimer's flies were then crossed to to three different UAS-RNAi lines (rescue groups) and tested for lifespan and movement characteristics. At ~21 days of age, flies were treated with CO_2 and then placed in a dark chamber for 30 mins. Flies were then placed individually in a circular 17 mm diam open-field arena, and movements were recorded for 5 mins with an overhead camera. Each fly's movements were later converted to x,y coordinates at 3 fps (Ethovision). A movement analysis was conducted to compare the organization and kinematic properties of flies' movements among rescue and Alzheimer's groups. Movements were first sorted into short, medium, and long progressions, and total distance, peak speed, path circuity, number of stops, and duration of stops were analyzed separately with custom analysis software (Excel). A separate one-way between-groups ANOVA was performed for each measure. The three rescue groups' lifespans approached those of normal flies, whereas the Alzheimer's groups were significantly shorter. The rescue groups also showed significantly greater peak speeds during long and short progressions than Alzheimer's groups, and showed significantly longer average distances during long progressions, relative to Alzheimer's flies. These results suggest that the rescue procedure is able to restore the lifespan and movement abilities in flies that have a genetic predisposition for movement deficits.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.03/C45

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

Support: R01AG063175
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R01MH116281
R01MH106575

Title: Chromatin accessibility mapping of functional Alzheimer's disease variants illuminates microglia-specific effects of PICALM on lipid droplet accumulation and phagocytosis

Authors: *A. KOZLOVA[1], S. ZHANG[1], A. SUDWARTS[2,3], H. ZHANG[1], S. SMIRNOU[2,3], X. SUN[4], K. STEPHENSON[1], X. ZHAO[1], B. JAMISON[1], M. PONNUSAMY[2,3], X. HE[4,6], Z.-P. PANG[7], A. SANDERS[1,5], H. J. BELLEN[8], G. THINAKARAN[2,3], J. DUAN[1,5];
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Abstract: Despite genome-wide association studies (GWAS) of late-onset Alzheimer's disease (LOAD) having identified a plethora of 75 genetic risk loci, the disease causal mechanism underlying most GWAS risk loci remains largely unknown. Determing putative causal disease variants and functionally linking risk alleles to LOAD-relevant cellular phenotypes has been a major challenge. Leveraging our recent approach for identifying functional GWAS risk variants showing allele-specific open chromatin (ASoC), we systematically identified putative causal LOAD risk variants in different subtypes of neurons, astrocytes and microglia (MG) derived from human induced pluripotent stem cells (iPSC), and established a causal link between a *PICALM* risk allele to heretofore unappreciated MG-specific role of *PICALM* in phagocytosis and lipid droplet (LD) accumulation. Our ASoC mapping uncovered functional risk variants for 26 LOAD risk loci, most of which were MG-specific. At the *PICALM* locus, the LOAD risk allele of the ASoC SNP rs10792832 altered chromatin accessibility to a PU.1 binding site and reduced *PICALM* expression in MG, impairing uptake of amyloid beta (Aβ) and myelin debris. Transcriptomic profiling of MG carrying the *PICALM* risk allele not only supported abnormal uptake, but also revealed transcriptional enrichment of pathways related to cholesterol synthesis and LD formation. Genetic and pharmacological perturbations in MG further established a causal link between *PICALM* risk allele and *PICALM* reduction, LD accumulation, and phagocytosis deficits. Our work elucidates a MG-specific role of *PICALM* in regulating lipid/cholesterol

accumulation that is potentially linked to LOAD pathophysiology, providing a functional neurobiological basis for developing novel clinical interventions.

Disclosures: A. Kozlova: None. **S. Zhang:** None. **A. Sudwarts:** None. **H. Zhang:** None. **S. Smirnou:** None. **X. Sun:** None. **K. Stephenson:** None. **X. Zhao:** None. **B. jamison:** None. **M. Ponnusamy:** None. **X. He:** None. **Z. Pang:** None. **A. Sanders:** None. **H.J. Bellen:** None. **G. Thinakaran:** None. **J. Duan:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.04/C46

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

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George and Anne Ryan Institute for Neuroscience, University of Rhode Island
College of Pharmacy, University of Rhode Island
Interdisciplinary Neuroscience Program, University of Rhode Island
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RI-INBRE SURF Program, University of Rhode Island

Title: The role of DNA damage-induced epigenetic alterations in age-related cognitive decline and Alzheimer's disease

Authors: *S. BARTMAN, L. GASPAR, H. TOBIAS-WALLINGFORD, D. HUNTER, G. COPPOTELLI, J. M. ROSS;
George and Anne Ryan Inst. for Neurosci.; Col. of Pharm., Univ. of Rhode Island, Kingston, RI

Abstract: Recent decades have witnessed a dramatic increase in human longevity, which has contributed to higher prevalence of age-related diseases including brain aging disorders, such as Alzheimer's disease (AD). The aging process is accompanied by an accumulation of damage to macromolecules, organelles, and cells, which ultimately leads to organ/tissue dysfunction and death. Although the precise cause of the aging process is unknown, epigenetic alterations and deregulation of gene expression have been implicated in playing a role. Using the innovative ICE (inducible changes to the epigenome) mouse model together with the well-characterized APP/PSEN1 (APP/PS1) mouse, we are directly testing, for the first time, whether epigenetic alterations induced by DNA damage, can affect the onset and progression of AD pathology in "DICE" (dementia from inducible changes to the epigenome) mice. A battery of behavioral testing is ongoing to compare possible cognitive changes in DICE mice with APP/PS1, ICE, and CRE controls. Preliminary results thus far indicate that male and female DICE mice move significantly more and with faster speed than controls, when assessing spontaneous locomotion

and anxiety-like behavior in the open-field and light/dark preference behavioral assays. Moreover, male and female DICE mice demonstrated less ability to recall the target hole of the Barnes Maze when evaluated for spatial memory. Using the startle reflex behavioral assay to evaluate brainstem functioning, both male and female DICE mice exhibited a larger motor response following various auditory stimuli, as compared to controls. Ongoing studies aim to characterize and quantify Aβ; plaque formation as well as gliosis and microglial expression in brains from DICE mice as compared to APP/PS1 controls using immunohistochemistry, western blot, ELISA, and qPCR. These findings will provide valuable insights into the etiology of Alzheimer's disease, especially as it pertains to the role of epigenetics.

Disclosures: S. Bartman: None. **L. Gaspar:** None. **H. Tobias-Wallingford:** None. **D. Hunter:** None. **G. Coppotelli:** None. **J.M. Ross:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.05/Web Only

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

Support: STI2030-Major Projects-2022ZD0211800
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Fundamental Research Funds for the Central Universities (Peking University Medicine Fund for world's leading discipline or discipline cluster development, BMU2022DJXK007)

Title: Dietary fat intake contributes to the risk of Alzheimer's disease: a Mendelian randomization study

Authors: *Y. ZHU;
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Abstract: Background Observational studies showed a controversial relationship between dietary fat intake and Alzheimer's disease (AD), while the causal effects were unclear. **Aims** We aimed to assess the causal effects of total fat, saturated fat (SF), and polyunsaturated fat (PUF) intakes on AD. **Methods** A two-sample Mendelian randomization (MR) was performed by leveraging the genome-wide association studies (GWAS) of different types of fat intake from

UK Biobank (n=51,413), late-onset AD (LOAD, 4,282 cases, n=307,112) and total AD (6,281 cases, n=309,154) from FinnGen consortium. In addition, a multivariable MR (MVMR) was conducted to estimate the effects independent of carbohydrate and protein intakes (Figure 1). **Results** Genetically predicted per standard deviation increase in the total fat and SF intakes were associated with 44% and 38% higher risks of LOAD (total fat: odds ratio [OR]=1.44, 95% confidence interval [CI]: 1.03, 2.02; SF: 1.38 [1.002, 1.90]). The associations remained significant in the MVMR. Besides, total fat and SF intakes were associated with total AD in the MVMR, the corresponding ORs (95%CIs) were 2.09 (1.22, 3.57) and 1.60 (1.01, 2.52). Meanwhile, PUF intake was not associated with AD (Figure 2). **Conclusions** The present MR study indicated that total dietary fat intake, especially SF intake, contributed to the risk of AD, and the effects were independent of other nutrients. These findings informed prevention strategies and management for AD directly towards reducing dietary SF intake.

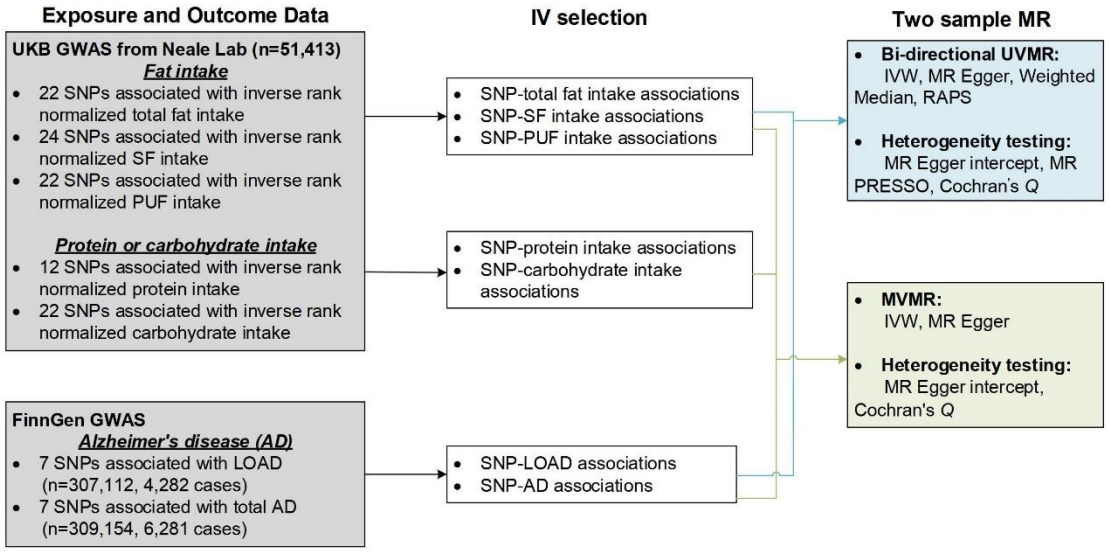

Figure 1. A flowchart of MR study design.
Notes: SF, saturated fat, PUF, polyunsaturated fat, LOAD, late-onset Alzheimer's disease, AD, Alzheimer's disease. MR, Mendelian randomization. IV, instrumental variables. UVMR, univariable MR. MVMR, multivariable MR with adjusting for protein and carbohydrate intakes. IVW, inverse variance weighted. RAPS, MR.robust adjusted profile score. SNP, single nucleotide polymorphism.

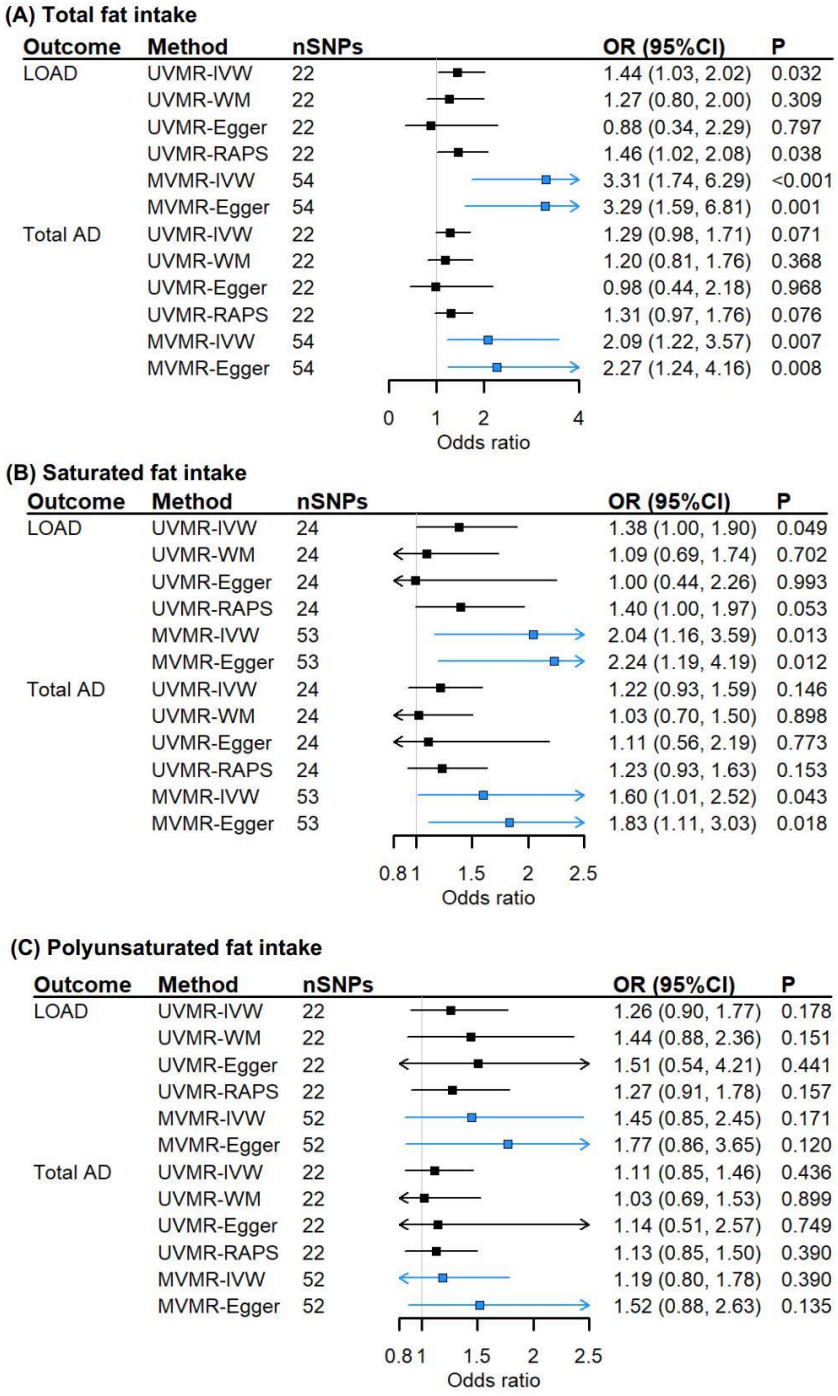

Figure 2. Univariable and multivariable MR analysis for the causal relationship of different types of fat intakes on Alzheimer's disease.
Notes: LOAD, late-onset Alzheimer's disease, AD, Alzheimer's disease, UVMR, univariable MR. MVMR, multivariable MR with adjusting for protein and carbohydrate intake. IVW, inverse variance weighted. RAPS, MR.robust adjusted profile score. SNP, single nucleotide polymorphism. OR, per one-fold increase in the odds of the total AD or LOAD, on the increase of the corresponding fat intake. CI, confidence interval.

Disclosures: Y. Zhu: None.

Poster

PSTR446: Alzheimer’s Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.06/C47

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

Title: Global DNA methylation and its correlation with cognitive impairment in women with probable sporadic Alzheimer's disease.

Authors: *C. MARIN ARANDA[1], S. ZAINA[1], N. HERNÁNDEZ SEBASTIÁN[2], M. CARDONA ALVARADO[1], M. GUERRERO VILLALPANDO[1], M. SOLIS-ORTIZ[3]; [1]Med. Sci., Univ. de Guanajuato, León, Mexico; [2]Optics Res. Ctr., León, Mexico; [3]Dept. de Ciencias Médicas, Univ. of Guanajuato, Leon, Mexico

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder that leads to cognitive impairment, particularly episodic memory. DNA methylation is an epigenetic mechanism, which has been related to the etiology of AD, but its influence on global cognition and episodic memory is not widely known. The aim of this study was to investigate global DNA methylation in leukocytes of women with probable sporadic AD and its correlation with the episodic memory. Forty women between 65 and 80 years old participated in the study. The women were classified into three study groups according to the MoCA test classification: mild cognitive impairment, moderate cognitive impairment, and severe cognitive impairment or probable AD. Episodic memory, a domain of the MoCA test, was analyzed among the three study groups. DNA from peripheral blood leukocytes was used to analyze global DNA methylation. Quantification of global DNA methylation was determined using the commercial Methylflash® kit. The group of women with severe cognitive impairment or probable AD showed global DNA hypomethylation compared to the mild cognitive impairment group. Global DNA hypomethylation was positively correlated with episodic memory.These findings suggest that DNA hypomethylation appears to influence episodic memory deficits, indicating that older women showed an inability to recover memory of past events.

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Poster

PSTR446: Alzheimer’s Disease: Genetics

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

Support: This work was supported by the Advancing a Healthier Wisconsin Endowment projects 5520482 and 5520760, as well as the Academic Enrichment Fund from the Department of Cell Biology, Neurobiology, and Anatomy at the Medical College of Wisconsin.

Title: Role of late-onset Alzheimer's disease-associated genes in aging

Authors: *S. G. WAGHMARE[1], A. FRANITZA[1,2], L. E[1];
[1]Cell Biology, Neurobio. and Anat., [2]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Role of Late-onset Alzheimer's Disease-Associated Genes in Aging
Swapnil Gorakh Waghmare[1,2], Ariel Franitza[1], Lezi E[1,2]
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Genome-wide association studies have identified numerous potential genetic variants and target genes associated with late-onset Alzheimer's disease (LOAD), yet the precise 'AD-relevant' roles and mechanisms of many of them remain unknown. Age is the primary risk factor for developing LOAD, making it crucial to investigate the potential involvement of these LOAD-associated genes in aging. However, investigating this in mammalian models is a time-intensive process. Here, we address this question by utilizing the model organism *Caenorhabditis elegans* which have a more manageable lifespan in laboratory settings and orthologs to many of the LOAD-associated genes. For initial screening, we prioritized genes, including *acn-1*/ACE, *amph-1*/BIN1, *aph-1*/APH1B, *unc-11*/PICALM, *abi-1*/ABI3, *ech-2*/ECHDC3, *tbc-17*/USP6NL, and *unc-112*/FERMT2. The focus on these genes is driven by their exclusive expression in the *Caenorhabditis elegans* nervous system, justifying the relevance of studying their potential involvement in neuronal aging. We used adulthood-specific systemic RNA interference (RNAi) to knockdown individual LOAD-associated genes to examine the effects on lifespan. Our preliminary findings show that *aph-1* and *abi-1* RNAi treatments showed no significant alteration in lifespan compared to controls. Furthermore, there was a slightly decreased lifespan in *acn-1* and *amph-1* knockdowns, a significant decrease in *unc-11*, and slight increases in *abi-1*, *ech-2*, *tbc-17*, and *unc-112* knockdowns compared to controls. LOAD-associated genes that do not affect lifespan may illuminate their specific roles in neurodegeneration, potentially providing direct insights into AD-relevant pathology. Conversely, genes that do impact lifespan might suggest broader roles in overall aging, requiring careful examination to disentangle between lifespan-related effects and their inherent impact on neuronal health. Therefore, exploring the role of these LOAD-associated genes in neuronal morphology, physiology, and memory function could enhance our understanding of their involvement in age-associated neurodegeneration.

Disclosures: S.G. Waghmare: None. **A. Franitza:** None. **L. E:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.08/C49

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

Support: Simons Foundation 984481
NIA 7RF1AG063755-02

Title: Hippocampal dendritic spine morphometry signatures of cognitive resilience to Alzheimer's disease

Authors: *T. STEVENSON[1], M. BERCHULSKI[2], S. J. MOORE[1], C. C. KACZOROWSKI[2]; [1]Neurol., Univ. of Michigan, Ann Arbor, MI; [2]Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Background: While dendritic spine loss is an established phenotype of normal aging and Alzheimer's disease (AD) pathology, few studies have examined the relationship between spine loss and cognitive resilience in normal aging and AD. In one study, significant reductions in spine density were observed for patients with cognitive impairment and AD pathology, but spine density was similar between cognitively normal control patients and cognitively normal patients with AD pathology (patients with cognitive impairment but no AD pathology were not included in the study). These data provide evidence to support the hypothesis that resilience to dendritic spine loss protects against cognitive decline due to AD. The mechanisms that underlie this resilience, however, are unknown. Accordingly, the genetically diverse, but fully isogenic, AD-BXD mouse panel will be used to identify genetic variants that confer resilience to spine loss in cognitively resilient and susceptible AD-BXD strains. The AD-BXD panel incorporates five high-risk familial AD mutations (APP K670N/M671L [Swedish] + I716V [Florida] + V717I [London] and PS1 M146L+ L286V) on different strains from the BXD reference panel (BXD; C57BL/6J x DBA/2J). Methods: Four AD-BXD strains were chosen based on their cognitive memory performance at 14 months of age in the contextual fear conditioning paradigm (cognitively resilient: AD-BXD99 and AD-BXD124; cognitively susceptible: AD-B6 and AD-B6xD2). Hippocampal neurons from 14-month-old female AD-BXD and Ntg-BXD mice were filled with biocytin during electrophysiological recording and subsequently stained with streptavidin-488. High-resolution images (0.036μm x 0.036μm x 0.13μm) were acquired with a Leica Stellaris 5 confocal microscope (63x, 1.4 NA), and dendritic spines were reconstructed and processed using Neurolucida 360 (v2024.1.1)/Neurolucida Explorer (v2024.1.1), respectively. All data were statistically analyzed and graphed using R Studio or GraphPad Prism 10.0. Results: Spine morphometry and density data were collected from the four AD-BXD strains and their Ntg-BXD counterparts. While preliminary interim analysis of the B6 strain found no differences between AD-B6 and Ntg-B6 mice with respect to morphometry parameters, including backbone length, volume, or head diameter, a suggestive decrease in spine density was observed. Conclusions: Taken together, spine morphometry and density data from the AD-BXD99, AD-BXD124, AD-B6, and AD-B6xD2 strains will allow future analyses to determine the genetic contributions to spine morphometry and its relationship to cognitive resilience in AD.

Disclosures: T. Stevenson: A. Employment/Salary (full or part-time):; University of Michigan. **M. Berchulski:** A. Employment/Salary (full or part-time):; University of Michigan. **S.J. Moore:** A. Employment/Salary (full or part-time):; University of Michigan. **C.C. Kaczorowski:** A. Employment/Salary (full or part-time):; University of Michigan.

Poster

PSTR446: Alzheimer’s Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.09/C50

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

Title: Paris is involved in tau pathology and astrogliosis in alzheimer's disease by regulating the transcription of stat3

Authors: *J.-Y. SONG, S. KANG, V. L. DAWSON, T. M. DAWSON;
Johns Hopkins, Baltimore, MD

Abstract: PARIS, initially identified as a substrate of Parkin, has been reported to accumulate in Parkinson's disease (PD) and contribute to the acceleration of disease progression. Here, we demonstrate that PARIS is implicated in the pathogenesis of Alzheimer's disease (AD) in addition to PD, exacerbating tau pathology and astrogliosis by elevating the transcriptional activity of STAT3. Previous studies have shown that treating AD model mice with STAT3 inhibitors improves their behavioral defects, neuroinflammation, and pathological indicators. However, research on the underlying mechanism was lacking. Genetic depletion of PARIS prevents tau pathogenesis and behavioral deficits in the tau mouse model. On the other hand, transgenic mice overexpressing PARIS exhibit AD phenotypes such as increased tau phosphorylation, gliosis, and memory loss, and these effects were found to be rescued by administration of a STAT3 inhibitor. Our findings could provide mechanistic insights that may be essential for developing treatments for neurodegenerative diseases targeting the PARIS-STAT3-GFAP axis.

Disclosures: J. Song: None. **S. Kang:** None. **V.L. Dawson:** None. **T.M. Dawson:** None.

Poster

PSTR446: Alzheimer’s Disease: Genetics

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Program #/Poster #: PSTR446.10/C51

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

Support: RS-2023-00217123
2022R1A2C1002984

Title: The specific class of noncoding RNA has regulatory function in Alzheimer's disease

Authors: *S. YANG;
Hanyang Univ., 안산, Korea, Republic of

Abstract: Many research on noncoding RNAs (ncRNAs) in the physiological mechanisms have been accumulating, whereas the function of specific class of noncoding RNA including small nucleolar RNAs (snoRNAs) and their subset small Cajal body-specific RNAs (scaRNAs) in neurodegenerative disorders remain yet to be elucidate. Here, the scaRNA has shown notable alteration in the cortical region of brain from Alzheimer's disease condition of 5xFAD mouse model among snoRNA genes, thereby we hypothesize that the scaRNA may participate in the pathophysiological process of Alzheimer's disease. To identify the scaRNA-involved regulatory mechanism, high-throughput total RNA sequencing and analysis has been performed with the scaRNA overexpressed neuroblastoma cell line. Compare to the 5xFAD mice and scaRNA overexpressed cell-derived gene dataset, the intersection of genes has been sorted in differential expression analysis. The gene ontology (GO) analysis has described that those gene sets have specific features of the innate immune system and immune-effector processes. These findings could provide that the scaRNA might have ability as an important mediator in Alzheimer's disease progression and be a potential pharmaceutical candidate.

Disclosures: S. Yang: None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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

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Brightfocus Foundation research grant A20201159S
Brightfocus Foundation research grant A2022036S
KU career development grant 2302009
NIH grant P30 AG072973

Title: Hippocampal transcriptome-wide association study of mitochondrial solut carriers in Alzheimer's disease

Authors: *J. TIAN[1], K. JIA[2], T. WANG[3], L. GUO[4], E. K. MICHAELIS[5], R. H. SWERDLOW[6], H. DU[7];
[1]Univ. of Kansas, Lawrence, KS; [2]Pharmacol. and Toxicology, The Univ. of Kansas, Lawrence, KS; [3]Pharmacol. & Toxicology, The Univ. of Kansas, Lawrence, KS; [4]Pharmacology&Toxicology, The Univ. of Kansas, Lawrence, KS; [5]Dept Pharmacol & Toxicol, Univ. Kansas, Lawrence, KS; [6]Dept Neurol, Univ. Kansas Sch. Med., Leawood, KS; [7]Dept. of Pharmacol. and Toxicology, and Higuchi Biosci. Ctr., The Univ. of Kansas, Lawrence, KS

Abstract: The significance of mitochondrial dysfunction in the pathogenesis of Alzheimer's disease (AD) is well-recognized, while the relationship between mitochondrial function and genetic variability is still largely unknown. Solute carriers family 25 (SLC25) is a mitochondrial-specific sub-family of solute carriers that transport molecules including inorganic ions, nucleotides, amino acids, and enzyme cofactors, as well as Krebs cycle metabolites across the mitochondrial membrane. The significance of these SLC25 substrates in mitochondrial biology and hippocampal function, especially the role of *SLC25*-related genetic traits remains incompletely understood. Taking the advantage of the newly developed tissue-specific transcriptome-wide association study (TWAS) analysis, we explored the genetic association between *SLC25* genes and AD through three independent AD cohorts, revealing three AD-susceptibility genes including *SLC25A10*, *SLC25A17*, and *SLC25A22*. By incorporating neuroimaging data and hippocampal TWAS-predicted gene expression, the result highlights a negative correlation of *SLC25A22* with hippocampal atrophy rate in AD patients, surpassing the impacts of AD risk factors including sex, age, and Apolipoprotein E4 (*ApoE4*). Further analysis suggested an association between *SLC25A22* and AD onset, distinguishing it from the other two transcriptome-wide significant genes. Pathway and network analysis connected hippocampal *SLC25A22* downregulation with abnormalities in neuronal function and development, consistent with the enrichment of *SLC25A22* expression in human glutamatergic neurons. In this study, we identified AD-susceptibility genes in the *SLC25* family through genomic-based prediction of hippocampal gene expression. These findings offer mechanistic insights into the mitochondrial cascade hypothesis of AD, laying the groundwork for the future development of precision medicine diagnostic tools aimed at early AD prevention by targeting genes related to mitochondria.

Disclosures: J. Tian: None. **K. Jia:** None. **T. Wang:** None. **L. Guo:** None. **E.K. Michaelis:** None. **R.H. Swerdlow:** None. **H. Du:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.12/C53

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

Support: NIH 4K00NS125830-02

Title: Determining the functional relevance of PSEN2 3′UTR length in Alzheimer's disease.

Authors: *J. N. BRUTMAN, M. DE LEON, E. J. KAUFMAN, E. NIZAMIS, P. N. VALDMANIS;
Div. of Med. Genetics, Sch. of Med., Univ. of Washington, Seattle, WA

Abstract: Alzheimer's disease (AD), characterized by atypical build-up of amyloid beta (Aβ) peptide and tau proteins in the brain, is the most common form of dementia worldwide. The

onset of AD is highly variable. In 1-5% of all cases, AD has a familial genetic link (familial AD; fAD), while in the remaining cases, no genetic association is known (sporadic AD; sAD). Thus, understanding environment x gene interactions may help uncover the complex etiology of sAD. The Aβ peptide is formed following the cleaving of amyloid precursor protein by the gamma secretase complex, containing either presenilin 1 (PSEN1) or presenilin (PSEN2). Pathogenic variants in these genes are heavily implicated in fAD. Recent long-read RNA sequencing from the Valdmanis group revealed cryptic exon inclusion in *PSEN2* and differential regulation of its 3′ untranslated region (3′UTR) in sAD. Interestingly, 2/3 of sAD reads harbored the canonical short 507 bp *PSEN2* 3'UTR, while 1/3 of sAD reads utilized a long 3976 bp *PSEN2* 3'UTR. The 3′UTR promotes transcriptional diversity in neurons by regulating maturation, stability, and localization of newly generated RNA transcripts. The extended *PSEN2* 3′UTR contains additional microRNA binding sites and regulatory elements. Thus, the goal of this study was to determine the functional significance of *PSEN2* 3′UTR length *in vitro*. We designed 4 different constructs: a control construct, a construct containing only the *PSEN2* coding region and no 3′UTR (*PSEN2* CDS), a construct containing *PSEN2* with the short 3′UTR (*PSEN2* 3′UTR S), and a construct containing *PSEN2* with the long 3′UTR (*PSEN2* 3′UTR L). We then overexpressed these constructs in either HMC3 human microglial or SH-SY5Y human neuroblastoma cell lines and quantified relative overexpression utilizing qPCR with primers specifically designed to capture the CDS region and short 3'UTR, or the long 3'UTR. We found that transfection of HMC3 or SH-SY5Y cells with the *PSEN2* CDS, 3′UTR S, or 3′UTR L constructs increases overall *PSEN2* transcript abundance. Importantly, the *PSEN2* 3′UTR L construct had increased stability in cells; we observed an increase in the expression of the long *PSEN2* 3′UTR in cells transfected with the *PSEN2* 3′UTR L construct relative to the *PSEN2* 3′UTR S construct (HMC3: p=<0.0001, n=7-8/group; SH-SY5Y: p=<0.0001, n=7/group). These results demonstrate the establishment of a functional system to test differences in genetic regulation, APP processing, and subcellular localization between the short and long *PSEN2* 3′UTRs. Elucidating the functional significance of *PSEN2* 3′UTR regulation will further our understanding of *PSEN2* in AD.

Disclosures: J.N. Brutman: None. **M. de Leon:** None. **E.J. Kaufman:** None. **E. Nizamis:** None. **P.N. Valdmanis:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.13/C54

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

Support: NIH Grant GR021297

Title: Elucidating the interrelationship between sleep, DNA damage/repair, and Alzheimer's disease

Authors: *C. E. LOCKLEAR, A. CHANDLER, C.-H. VOLMAR, C. R. WAHLESTEDT; Psychiatry and Behavioral Sci., Univ. of Miami Miller Sch. of Medicine, Ctr. for Therapeut. Innovation, Miami, FL

Abstract: Alzheimer's disease (AD) is the most common form of dementia and affects around 6.5 million individuals in America with a total healthcare cost of $321 billion. AD is characterized by cognitive dysfunction, memory impairment, and disrupted sleep. Sleep disruption is linked to poor cardiometabolic health, but recent evidence emphasizes the importance of sleep as a mediator of genetic stability. During wakefulness, DNA damage (in the form of single-strand and double-strand breaks) accumulates in neurons. Inversely, during sleep, DNA repair enzyme activity increases, which decreases DNA damage in neurons. DNA damage in neurons can lead to neuronal cell death, which is a cause of neurodegeneration (i.e., neurodegenerative diseases such as AD). Total sleep deprivation results in exacerbated levels of DNA damage and impaired DNA repair enzymes in neurons, but the role of specific sleep stages in this process is unclear, especially in the context of AD. This study aims to fill this gap by utilizing a novel system of sleep deprivation in mice to explore the underlying mechanisms connecting sleep, neuronal DNA damage/repair, and AD. This study utilized a combination of DSI Co. wireless telemetry, Spike-2 software from CED Co., and third-party olfactory controllers to achieve automatic sleep deprivation via air-puffs. C57BL/6J (B6) mice were utilized for validation of the behavioral state recording/sleep deprivation system and preliminary biological analyses. The system was employed to achieve sleep deprivation in mice for ~8 hours, then blood and brain tissue were collected for subsequent epigenetic and proteomic analysis. qPCR and western blot were then applied, in combination with inferential statistics, to determine the expression of AD-related targets of interest. Behavioral state recordings indicate the system can accurately collect and analyze telemetry signals in real time then initiate an air-puff to wake the animal, which successfully achieves sleep deprivation. qPCR and western blot results indicate a significant decrease in DNA damage repair enzyme and an increase in inflammatory cytokine expression, relative to controls, following ~8 hours of sleep deprivation ($p<0.05$). These preliminary results indicate this novel system of sleep deprivation in mice can be applied to elucidate DNA damage/repair mechanisms in relation to sleep and AD. Future studies will utilize this system (and an AD-mouse model) to explore specific sleep stages in relation to AD-progression. They will also extend the genetic analyses through leveraging SSiNGLe, a novel technique designed and implemented by our group for analyzing DNA single-strand breaks.

Disclosures: C.E. Locklear: None. **C. Volmar:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.14/C55

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

Support: NIH Grant R01 AG070214
NIH Training Grant T32 NS082145

Title: Investigating the role of CELF2 in regulating alternative splicing of MAPT on AD-associated phenotypes

Authors: *I. N. SYED[1,2], X. LI[3,4], R. ADHIKARI[3,4], Z. ZHANG[5], Z. LIU[5], L. CHEN[3,6,4];
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Abstract: Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disease caused by a combination of genetic, environmental, and lifestyle factors. As of 2024, about 7 million individuals in the United States alone are living with AD. Current therapeutic options available merely manage symptoms, rather than preventing disease progression. Although there are drugs available that treat beta-amyloid pathology early in AD to slow cognitive decline, these drugs fall short of a cure or preventative intervention for AD. Genetic factors are well established to contribute to the risk of developing AD, as the heritability of late-onset AD is over 70%. Among such genetic risk factors is the recently identified gene encoding an RNA binding protein, CUGBP Elav-like family member 2 (*CELF2*). *CELF2* regulates tissue-specific alternative splicing, particularly within the central nervous system. Alternative splicing affects over 95% of genes in the human genome, contributing to the functional diversity and complexity of proteins. Disruption of mRNA splicing has been linked to age-associated neurodegeneration, including AD. A recent study examined alternative splicing events in a large dataset of aging brains and identified aberrant alternative splicing events associated with AD. We performed CLIP-seq and identified *CELF2* binding motifs that are enriched in AD-associated aberrant splicing events, supporting that dysregulation of *CELF2* contributes to the aberrant splicing of genes associated with AD. We further observed that mRNAs previously identified as genetic risk factors for Alzheimer's disease, including *APP, MAPT, PSEN1, PSEN2, and BIN1,* are directly bound by *CELF2*. Currently, we are investigating the mechanisms by which *CELF2* controls alternative splicing of AD-related genes and how they contribute to AD phenotypes. Our findings will open new horizons for the targeting of genes responsible for neuronal aging as an ideal therapeutic target against age-associated neurodegenerative disease.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.15/C56

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

Support: 1RF1AG071683
3U19AG068054-02S
U54 AG054349-06

Title: Spatial and single-nucleus transcriptomics : Insights into Alzheimer's disease

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Abstract: The molecular etiology of Alzheimer's disease (AD), influenced by both environmental and genetic factors, remains elusive. Our study combines spatial transcriptomics (ST) and single-nucleus RNA sequencing (snRNA-seq) to examine the transcriptomic landscape of late-onset sporadic AD and AD associated with Down Syndrome (AD in DS). Investigating AD in DS offers a unique perspective that may bridge the understanding gap between traditional genetic mouse models and sporadic AD. Our analysis highlights significant transcriptomic alterations, potentially underlying the disease-specific pathology observed preferentially in certain cortical layers. We discovered temporally transient and spatially confined disease processes through spatial co-expression network analysis, including a dysregulated glial inflammatory gene module in the upper cortical layers linked to genetic risk factors and amyloid-associated pathways in AD. This study also explores cell-cell communication disruptions, emphasizing the role of specific genes within this inflammatory module in perturbed signaling networks. Additionally, we generated ST data from an amyloid-focused AD mouse model, facilitating a cross-species comparison to pinpoint amyloid-proximal transcriptomic changes within a specific conformational context. This research underscores the importance of integrating cellular and spatial resolution in studying AD, revealing intricate transcriptomic variations across different stages and forms of the disease, which are crucial for understanding AD pathogenesis and identifying potential therapeutic targets.

Disclosures: S. Morabito: None. **E.E. Miyoshi:** None. **C.M. Henningfield:** None. **S. Das:** None. **N. rahimzadeh:** None. **E. Head:** None. **K.N. Green:** None. **V. Swarup:** None.

Poster

PSTR446: Alzheimer’s Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.16/C57

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

Support: NIH NIA Grant R01AG066179
NIH Grant R01AG021155
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Department of Neurological Surgery, University of Wisconsin-Madison School of Medicine
NIH NINDS T32NS105602

Title: Whole genome blood DNA methylation levels identified in Alzheimer's Disease are extensive, sex-specific, and predictive of diagnostic stages

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Abstract: Late-onset dementia due to Alzheimer's disease (AD) is the most common neurodegenerative disease that includes a prodromal stage, mild cognitive impairment (MCI). Evidence suggests that environmental influences increase the risk of AD in part through interactions with the epigenome, particularly DNA methylation (Santana *et al.*, 2023, Liu *et al.*, 2018). Using whole genome methylation sequencing to interrogate the entire human blood methylome (over 25 million sites), we identified 28,038 differentially methylated positions (DMPs) in AD (Breen *et al.*, 2024). Here we hypothesize that differential DNA methylation levels play a role in prodromal stages of AD. To test this hypothesis, we extend this research by integrating whole genome methylation data from the blood of MCI participants (*N*=99) into a three-way pairwise interaction model with matched AD (*N*=109) and cognitively unimpaired (CU, *N*=174) participants and found 1,743, 2,929, and 1,847 differentially methylated genes in each pairwise comparison (MCI *vs.* CU, AD *vs*. MCI, AD *vs*. CU, respectively). Pathways analysis of differentially methylated genes between all comparisons shows enrichment for biologically relevant terms related to AD such as synapse organization, regulation of neurotransmitter levels, and ion transmembrane transport. In addition, we identified enrichment for mitochondrial-related genes, including glucose/carbohydrate metabolism (MCI *vs*. CU), oxidative stress (AD *vs*. MCI), and fatty acid metabolism/beta-oxidation (AD *vs*. CU), as well as epigenetic processes (*e.g.*, histone posttranslational modification genes). Since AD has a sex-biased incidence, with females comprising nearly two thirds of all cases, we next investigated sex-specific DNA methylation levels and found that less than 26% and 20% of differentially methylated genes were shared between both sexes in MCI and AD, respectively. Moreover, pathways analyses only found an enrichment of terms related to cognitive decline among female-specific genes from all comparisons. Finally, we employed machine learning algorithms and unsupervised hierarchical clustering to identify the top twenty most distinguishing differentially methylated positions, which were able to stratify all 391 participants by diagnostic group. Together, these data highlight extensive differential blood DNA methylation levels in MCI and

AD on genes with known and novel roles in cognitive decline that are sex-specific and could be useful as biomarkers to predict MCI and AD diagnosis.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.17/C58

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

Support: RF1AG078660
R01AG057339

Title: Systems genetic dissection of Alzheimer's disease brain gene expression networks

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Abstract: In Alzheimer's disease (AD), changes in the brain transcriptome are hypothesized to mediate the impact of neuropathology on cognition. Gene expression profiling from postmortem brain tissue is a promising approach to identify causal pathways; however, there are challenges to definitively resolve the upstream pathologic triggers along with the downstream consequences for AD clinical manifestations. We have functionally dissected 30 AD-associated gene coexpression modules using a cross-species strategy in *Drosophila melanogaster* models. First, integrating longitudinal RNA-sequencing and fly behavioral phenotyping, we interrogated unique and shared transcriptional responses to amyloid beta (Aβ) plaques, tau neurofibrillary tangles, and/or aging, along with potential links to progressive neuronal dysfunction. Our results highlight hundreds of conserved, differentially expressed genes mapping to AD regulatory networks. In order to confirm causal modules and pinpoint AD network drivers, we next performed systematic *in vivo* genetic manipulations of 357 conserved, prioritized targets, identifying 144 modifiers of Aβ- and/or tau-induced neurodegeneration. We subsequently partitioned candidate causal subnetworks, which were further validated based on human or *Drosophila* genetic evidence. We discover an up-regulated, causal network that is significantly enriched for both AD risk variants and markers of immunity / inflammation, and which promotes Aβ and tau-mediated neurodegeneration based on fly genetic manipulations in neurons. By

contrast, a promising synaptic regulatory network is strongly downregulated in human AD and is enriched for loss-of-function suppressors of Aβ/tau, consistent with a potential compensatory response to glutamatergic excitotoxic brain injury. In sum, our cross-species, systems genetic approach establishes a putative causal chain linking AD pathology, large-scale gene expression perturbations, and ultimately, neurodegeneration.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.18/C59

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

Support: NIH GRANT AG053988

Title: Systematic analysis of biological processes reveals gene co-expression modules driving pathway dysregulation in alzheimer's disease

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Abstract: Alzheimer's disease (AD) manifests as a complex systems pathology with intricate interplay among various genes and biological processes. Traditional differential gene expression (DEG) analysis, while commonly employed to characterize AD-driven perturbations, does not sufficiently capture the full spectrum of underlying biological processes. Utilizing single-nucleus RNA-sequencing data from postmortem brain samples across key regions—middle temporal gyrus, superior frontal gyrus, and entorhinal cortex—we provide a comprehensive systematic analysis of disrupted processes in AD. We go beyond the DEG-centric analysis by integrating pathway activity analysis with weighted gene co-expression patterns to comprehensively map gene interconnectivity, identifying region- and cell-type-specific drivers of biological processes associated with AD. Our analysis reveals profound modular heterogeneity in neurons and glia as well as extensive AD-related functional disruptions. Co-expression networks highlighted the extended involvement of astrocytes and microglia in biological processes beyond neuroinflammation, such as calcium homeostasis, glutamate regulation, lipid metabolism, vesicle-mediated transport, and TOR signaling. We find limited representation of DEGs within dysregulated pathways across neurons and glial cells, suggesting that differential gene expression alone may not adequately represent the disease complexity. Further dissection of inferred gene modules revealed distinct dynamics of hub DEGs in neurons versus glia, suggesting that DEGs exert more impact on neurons compared to glial cells in driving modular dysregulations

underlying perturbed biological processes. Interestingly, we observe an overall downregulation of astrocyte and microglia modules across all brain regions in AD, indicating a prevailing trend of functional repression in glial cells across these regions. Notable genes from the CALM and HSP90 families emerged as hub genes across neuronal modules in all brain regions, suggesting conserved roles as drivers of synaptic dysfunction in AD. Our findings demonstrate the importance of an integrated, systems-oriented approach combining pathway and network analysis to comprehensively understand the cell-type-specific roles of genes in AD-related biological processes.

Disclosures: T. Adeoye: None. **G. Ullah:** None.

Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.19/C60

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

Support: R01AG081374
R01MH116281
R01MH106575
R01AG063175

Title: Alzheimer'S disease protective allele at clu locus promotes neuron excitability, neuron-glia lipid transfer and astrocytic lipid droplets accumulation

Authors: *X. ZHAO[1,2], Y. LI[3], S. ZHANG[1], A. SUDWARTS[4], H. ZHANG[1], A. KOZLOVA[1], Z.-P. PANG[5], A. SANDERS[1], G. THINAKARAN[6], J. DUAN[1,2];
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Abstract: Disease causal mechanism remains largely unknown for most GWAS risk loci, including the Clusterin (CLU) locus. A major challenge is how to identify causal disease variants/genes and illustrate their functional impacts in cell types relevant to Alzheimer's Disease (AD). Here, leveraging our recently developed approach to identify functional GWAS risk variants that show differential allelic chromatin accessibility, i.e., allele-specific open chromatin (ASoC) in human iPSC-derived disease-relevant cell types, we prioritized the putatively causal risk variant at CLU locus. We found that the noncoding AD risk SNP rs1532278 at the CLU locus showed strong ASoC in hiPSC-derived excitatory neurons (iGlut), but not in other type of neurons, microglia or astrocytes. To study the functional impacts of rs1532278, we carried out CRISPR/Cas9 editing to obtain isogenic iPSC lines that are

homozygous for the AD protective alleles (T/T) or risk alleles (C/C), and differentiated them into iGlut that were cocultured with mouse astrocytes (mAst). We found the CLU with T/T elevated neuronal CLU through enhanced chromatin accessibility to transcript factor ISL2 binding, and higher neuron CLU expression was correlated with more robust neuron excitability but paradoxically also with higher levels of Aβ and Tau (likely a byproduct of neural excitability). To gain insights into the underlying mechanisms, we performed transcriptomic analysis found that the enriched gene pathways in iGlut carrying the CLU T/T alleles not only supported an enhanced neuronal excitability but also suggested an interesting hypothesis: the neuron-specific effect of the AD protective allele may promote fatty acids (FAs) transfer from iGlut (thus neuron protective) to mAst. Consistently, we found that neuronal CLU/lipid particles in mAst and over 95% of LDs (Lipid Droplets) were accumulated in mAst, with T/T alleles associated with more LDs in LDs staining. Finally, we showed that mAst with LD accumulation when co-cultured with T/T iGlut exhibited more reactive oxygen species (ROS) and diminished glutamate uptake. Our study suggests the AD protective allele of rs1532278 at the CLU locus may act by altering chromatin accessibility and increasing neuronal CLU, which subsequently induces increased neuron excitability, and facilitates lipid neuron-glia trafficking and storage in the form of LD in astrocytes. Such neuron-CLU-mediated LD formation in astrocytes may help maintain astrocytic lipids and ROS hemostasis that provides the growth and energy need for maintaining proper neuronal excitability. This novel mechanistic insight will help us to understand how CLU promotes the risk of developing AD.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.20/C61

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

Support: NIH grant U19 AG074866
NIH grant R24 AG073190

Title: Deep molecular characterization of marmosets as a model of Alzheimer's disease

Authors: *G. CARTER[1], T. GUIMARÃES[2], D. DUONG[6], N. T. SEYFRIED[7], T. MURAI[8], H. HUHE[9], J. K. KOFLER[11], D. J. SCHAEFFER[3], J. PARK[2], A. THATHIAH[4], G. E. HOMANICS[12], P. L. STRICK[13], S. J. SUKOFF RIZZO[10], A. C. SILVA[5];
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Abstract: Alzheimer's disease (AD) is the most common form of dementia and will likely require early intervention for effective treatment. Its gradual progression and the inaccessibility of middle-aged brain tissue has limited the discovery of therapeutic strategies. The need for in vivo systems to study the underlying biological dysfunction and perform preclinical testing motivates establishment of new model systems with age-related molecular, imaging, and behavioral capacities. Here, we report on genetic, genomics, and proteomic analysis marmosets as a model of aging and dementia.

We have performed whole-genome sequencing on over 80 individual marmosets, including genetically engineered carriers of rare human variants of *PSEN1*. Data from genome-wide association studies was integrated to assess standing variation at risk loci for late-onset Alzheimer's disease using multiple sequence alignment and functional prediction. We assayed fibroblast cultures derived from mutant and age-matched wild type animals to identify AD-relevant gene and protein expression signatures. Plasma biomarkers were measured and association tests were performed for sex, age, and genotype.

We identified abundant standing genetic variation at multiple AD risk loci, with predicted non-synonymous variants in *ABCA7*, *CR1*, *SORL1*, *INPP5D*, and other candidate genes. High deleterious variant burden was detected in *BIN1* and *PTPRB*. We verified pedigree-based kinship structure and verified overall genetic diversity in our marmoset colony similar to that observed in human study populations. For gene and protein expression, we found the effects of *PSEN1* mutations mimicked the changes in cell lines derived from human AD cases relative to unaffected individuals. Blood biomarkers for neurofilament light and total Tau protein were strongly correlated across the population but only weakly associated with age, suggesting potential genetic influences.

Correlations between AD-relevant biomarkers in marmosets exceeded those observed in humans and were not determined by age, which suggests a genetic factors in the marmoset population may drive Alzheimer's signatures. Disease-like alterations in fibroblast gene and protein abundances further confirms the utility of the common marmoset as a model of Alzheimer's disease. These studies provide a roadmap for deep molecular analysis of aging marmosets as a model of dementia.

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Poster

PSTR446: Alzheimer's Disease: Genetics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR446.21/Web Only

Topic: C.01. Brain Wellness and Aging

Support: 2023 McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss
Research Education Component through Grant P30 AG066444

Title: Age-associated changes in organelle behavior and cytoskeleton structure in micro-RNA reprogrammed human neurons

Authors: *E. KLINMAN[1], A. YOO[2];
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Abstract: Age is the primary risk factor in the development of dementia and many other neurodegenerative conditions. However, modeling changes associated with age in human neurons is challenging. Neurons derived from induced pluripotent stem cells are stripped of their age-associated epigenetic signatures, and animal models cannot capture the complexity of the human proteome. The Yoo lab has pioneered a method to permit the study of aging in human neurons using microRNA to directly convert human skin fibroblasts into neurons (microRNA-induced neurons or miNs). These miNs retain the age-specific epigenetic and cellular properties of the donor fibroblast, enabling evaluation of healthy aging in neurons in vitro.
In this project we compare miNs from healthy young and old donors, focusing on the behavior of critical organelles and their reliance on the neuronal cytoskeleton. We identify age-related changes in the distribution of lysosomes, and relate this to decreased acidification of autophagosomes in neurites derived from older donors. We additionally characterize changes in mitochondrial dynamics, with advanced age favoring enhanced dynamic interactions between mitochondria. We observed that the distribution of the microtubule binding protein tau, which is involved in tauopathies such as Alzheimer's disease, changes with advancing age. Reducing tau expression in miNs from old donors reversed the phenotype of increased mitochondrial dynamics to levels observed in young donors.
Ongoing work seeks to determine what aspect of these changes may predispose individuals to sporadic Alzheimer's disease or other forms of age-related neurodegeneration.

Disclosures: E. Klinman: None. **A. Yoo:** None.

Poster

PSTR447: Alzheimer’s Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.01/C62

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

Support: NIH R21AG064479-01
NIH R25AG076396-01
UF McKnight Brain Institute and Department of Neuroscience

Title: Employing sexually dimorphic risk for metabolic syndrome to identify Alzheimer's disease risk-promoting or protective genes

Authors: *A. OJEDA[1], H. PIONTKIVSKA[2], H.-G. LEE[3], G. CASADESUS[4];
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Abstract: Employing sexually dimorphic risk for metabolic syndrome to identify Alzheimer's disease risk-promoting or protective genes
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Metabolic syndrome (MetS) is a central risk factor for Alzheimer's disease (AD) development. Notably, MetS evolves in a sexually dimorphic pattern, whereby males exhibit increased susceptibility to metabolic syndrome yet compared to females, are less likely to develop AD. The mechanisms that underlie the pathogenic link between MetS and AD remain poorly understood. However, the opposite sexually dimorphic patterns in MetS and AD development can be utilized to identify genes that confer AD risk or resilience in metabolically-stressed both sexes. To explore this link, we used male and female APP/PS1 mice, which mirror the sexually dimorphic pattern of AD development in the female human population and the human male's susceptibility for MetS, on a "Western" high-fat diet (HFD) or a control diet and longitudinally determined metabolic, AD-pathological, and hippocampal transcriptome responses. Our findings indicate a powerful CNS sexually-dimorphic transcriptomic response to MetS that is inverted to the observed degree of metabolic dysfunction. Females demonstrate an advanced disease state compared to males despite their relative physiological resilience to HFD. We also identified that the genes altered by HFD in males and females as different. Lastly, using machine learning unsupervised subset selection to identify genes linked to the observed metabolic and pathology changes in our mice, we identified several key genes implicated in AD development that showed sex differences. Together, these findings put forward novel genes and techniques to inform sex-specific AD treatment development.

Disclosures: A. Ojeda: None. **H. Piontkivska:** None. **H. Lee:** None. **G. Casadesus:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.02/C63

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

Title: Rna metabolism dysfunction in alzheimer's patients with tdp-43 co-pathology

Authors: *N. SHAJARIAN, A. LA SPADA;
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Abstract: Alzheimer's disease (AD) is characterized pathologically by extracellular amyloid-ß plaques and intracellular hyperphosphorylated tau tangles. Importantly, patients usually display at least one other co-pathology that can accelerate AD progression and/or worsen disease outcomes like cognition. Transactive response DNA binding protein 43 (TDP-43) mislocalization resulting in nuclear clearance and cytosolic aggregation is one such co-pathology. TDP-43 is primarily involved in RNA metabolism, binding pre-mRNA transcripts to coordinate mRNA processing. In amyotrophic lateral sclerosis (ALS), TDP-43 mislocalization is seen in ~97% of patients, and the resulting splicing and polyadenylation changes have been shown to contribute to ALS pathology. TDP-43 mislocalization is relatively understudied in AD, even though patients with this co-pathology (ADTDP) exhibit worsened cognitive impairment and more rapid disease progression. To investigate how TDP-43 mislocalization affects RNA metabolism in AD, we conducted a multi-faceted transcriptomics study, by taking advantage of the bulk RNA sequencing data from the Religious Order Study/Memory Aging Project that had recorded TDP-43 burden. We used various bioinformatics tools to investigate changes to mRNA expression (*DESeq2*), splicing (*Majiq*; *rMATS*; *Leafcutter*), and site of polyadenylation (*DaPars*) that differentiate ADTDP patients from AD patients without TDP-43 histopathology (ADnoTDP), in comparison to non-demented controls. We found that ADTDP patients have ~13 times more differentially expressed genes (DEGs), ~7 times more alternatively spliced (AS) genes, and ~1.5 times more alternative polyadenylation events than ADnoTDP patients. By ShinyGo analysis, DEGs and AS genes in ADTDP are implicated in pathways that have been implicated in AD pathogenesis, including synaptic health and mitochondrial function. It is possible some of these pathways may be disrupted to a greater degree when particular co-pathologies are also present. Because of this, these patients may not optimally respond to currently approved therapies; hence, understanding the role of co-pathologies, such as TDP-43, will be important rational development of future diagnostic tools and therapies.

Disclosures: N. Shajarian: None. **A. La spada:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.03/C64

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

Support: NIH RF1AG063540
NIH RF1AG051437
NIH 5T32-AG052354-07
Ellison Research Fund

Weill Neurohub
DIAN U19 AG032438

Title: Changes to peripheral immune cell proportions and gene expression in cognitively normal individuals with autosomal dominant Alzheimer disease pathogenic variants

Authors: *C. S. C. JOHNSON[1], A. COCHOIT[1], S. MAMDE[2], C. L. SMITH[1], K. J. GREEN[1], A. GROMOVA[3], A. R. LA SPADA[4], C. XIONG[5], C. M. KARCH[6], E. MCDADE[7], J. HASSENSTAB[8], A. M. FAGAN[8], C. CRUCHAGA[9], K. Z. LIN[10], A. M. GOATE[11], J. C. MORRIS[12], R. J. BATEMAN[12], T. D. BIRD[1], G. A. GARDEN[13], K. E. PRATER[1], S. JAYADEV[1];
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Abstract: Alzheimer's disease (AD) is the leading cause of decreased health span in people over age 65, affecting more than 40 million people worldwide. Deterministic variants in one of three genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) are responsible for AD in a subset of patients classified as having autosomal dominant AD (ADAD). Individuals with ADAD develop symptoms earlier than those with late-onset AD (LOAD), but the two groups share pathological features, suggesting a similar disease mechanism. ADAD presents an opportunity to understand AD etiology and identify biomarkers for early disease detection, as individuals with causative variants can be studied in a pre-symptomatic phase of disease. Here, we used bulk RNA sequencing to characterize gene expression in CD14+ peripheral blood mononuclear cells (PBMC) in a cohort of ADAD variant-carrying pre-symptomatic individuals (n = 24) and familial controls without disease-causing variants (n = 13). In parallel, we analyzed CD14+ PBMC gene expression in a cohort of individuals with LOAD (n = 22) and age-matched controls (n = 9). We found an effect of variant status on gene expression in pathogen response and metabolism-related genes in the ADAD cohort, when compared to familial controls. Some of these differentially expressed pathways were shared with the effect of LOAD compared to controls, while others were distinct. Within the ADAD cohort, amyloid β levels in the plasma and brain—well-known biomarkers of AD—were correlated with expression of genes related to metabolism and antiviral activity, respectively. We further explored the impact of variant status in all peripheral immune cell populations through single-cell RNA sequencing in cryopreserved PBMC in a cohort of 19 asymptomatic individuals (n = 10 *PSEN1* or *PSEN2* variant carriers,n = 9 healthy controls). We demonstrated changes in immune cell composition between AD variant carriers and controls as well as alterations in gene expression. One population of CD4+ T cells that are more abundant in variant carriers expressed interferon response genes and may emulate a population recently identified in sporadic early onset AD patients. A CD14+ monocyte population expanded in ADAD variant carriers showed increased expression of mitochondrial metabolism and cellular respiration genes. Taken together, these

findings suggest early changes in peripheral immune responses to ADAD progression that could be explored for biomarker development or as early points of intervention. Furthermore, these data potentially inform the shared immune responses in ADAD and LOAD that precede the onset of cognitive decline in AD progression.

Disclosures: C.S.C. Johnson: None. **A. Cochoit:** None. **S. Mamde:** None. **C.L. Smith:** None. **K.J. Green:** None. **A. Gromova:** None. **A.R. La Spada:** None. **C. Xiong:** None. **C.M. Karch:** None. **E. McDade:** F. Consulting Fees (e.g., advisory boards); Alzamend Neuro. **J. Hassenstab:** None. **A.M. Fagan:** None. **C. Cruchaga:** None. **K.Z. Lin:** None. **A.M. Goate:** None. **J.C. Morris:** None. **R.J. Bateman:** None. **T.D. Bird:** None. **G.A. Garden:** None. **K.E. Prater:** None. **S. Jayadev:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.04/C65

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

Title: Spatial transcriptomic profiling with 5xFAD mice

Authors: *S. XIA[1], S. CHEN[1], L. CHEN[2], Z. ZHAO[3];
[1]Zilkha Neurogenetic Institute, Univ. of Southern California, Los Angeles, CA; [2]Complete Genomics, San Jose, CA; [3]Physiol. and Neurosci., USC, Los Angeles, CA

Abstract: Alzheimer's disease (AD) is an age-dependent neurodegenerative disease that progressively deteriorates brain function, it is the most common form of dementia that impacting millions of people globally. The signature hallmarks of AD include amyloid plaques and Tau tangles, synaptic loss and neuronal dysfunction, vascular impairment, neuroinflammation and neurodegeneration. Although amyloid and Tau mediated proteinopathies have been considered as the main drivers, piling evidence from both patients and animal models have clear indicated that the disease is more complex at genetic, molecular, and cellular levels. Advancements in single-cell technologies have significantly refined our understanding of the molecular, cellular, and genetic traits in central nervous system (CNS). Spatial transcriptomics now offer unparalleled insights for spatial decoding of the pathologies and their impact on transcriptomics. In this study, we utilize a cutting-edge technology called spatial enhanced resolution omics-sequencing (Stereo-seq) to explore the regional differences and selective vulnerability among different brain cell types in Alzheimer's mouse model. This technique is based on DNA nanoball (DNB)-patterned array/chip and can generate whole-transcriptome maps of mouse brain unprecedentedly with a resolution up to 0.5 μm. More importantly, it is comparable with immunohistological procedures for pathological mapping on the same section. These advantages are unparalleled and particularly beneficial for mapping the regional and cell-type specific susceptible to amyloid or tau proteinopathies throughout the brain regions and over the disease progression. More importantly, we delved into the spatial interactions between different cell

types and A-beta plaque deposition at single cell resolution by employing a series of analysis pipeline. In conclusion, this work has demonstrated the potential of using the Stereo-seq technology as a powerful tool to investigate AD and other complex neurological disorders.

Disclosures: S. Xia: None. **S. Chen:** None. **L. Chen:** None. **Z. Zhao:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.05/C66

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

Support: T32AG061897
R01AG057931

Title: Identifying High-Risk for Alzheimer's Disease Subgroups: A Deep Embedded Clustering Analysis of Wisconsin Registry for Alzheimer's Prevention Participant Data

Authors: *C. TIRAMBULO[1], S. MERLINI[2], R. D. BRINTON[3], F. VITALI[2];
[1]Col. of Medicine/Medical Pharmacol., [3]Ctr. for Innovative in Brain Sci., [2]Univ. of Arizona, Tucson, AZ

Abstract: Individuals in the early stages of Alzheimer's disease (AD) constitute a heterogeneous group, with diverse risk factor profiles such as chromosomal sex, apolipoprotein E (APOE) genotype, and comorbidities, evolving over distinct time courses. Within a prodromal phase that can extend for one to three decades, opportunities and challenges exist in identifying crucial tipping points in progression and opportunities for prevention. Our study aimed to identify subgroups within the 389 individuals at high risk for AD (65.6±6.4 years old, 67.1% female, 38.8% APOE ε4 carriers) from the Wisconsin Registry for Alzheimer's Prevention data, 2001-2022. We analyzed prospectively collected data covering patient characteristics (age, sex, race, and APOE ε4 carrier status), medical history (history of diabetes, hypertension, and hyperlipidemia), plasma biomarkers (amyloid-β (Aβ) 40, Aβ42, Aβ40/42 ratio, phosphorylated tau (p-tau) 181, and p-tau 217), and blood laboratory parameters (insulin, glucose, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol). Employing classical clustering methodologies (CCMs, k-means (KMs), KMs with principal component analysis, hierarchical clustering (HC), and HC with dynamic time warping) to inform the unsupervised deep embedded clustering (DEC) algorithm, we evaluated cluster membership and assessed clinical validity. Variable contributions to the predicted cluster membership were assessed using SHapley Additive exPlanations values. Our DEC findings demonstrated promising results by identifying more distinct risk profile patterns for each cluster (n=8) compared to CCMs (n=2); achieving a more evenly distributed partitioning of participants into clusters with increased stability, measured by Jaccard and entropy scores; and validating the clinical recognizability based on laboratory values, plasma biomarkers, physician cognitive

diagnoses, and Preclinical Alzheimer Cognitive Composite scores. Cluster characterization revealed participants in cluster 6 (n=44) were most at-risk for AD, consisting of female APOE ε4 carriers with elevated p-tau levels. Conversely, cluster 4 (n=57) was the least at-risk, youngest cluster, comprising females with fewer comorbid conditions and the lowest AD biomarker levels. Cluster 3 (n=81) represented the control population. Going forward, these outcomes will enable a robust pipeline for integrating electronic medical record data, empowering diverse patient characterization, and better identify those at risk to implement personalized preventative treatment within heterogeneous populations at risk for AD.

Disclosures: C. Tirambulo: None. **S. Merlini:** None. **R.D. Brinton:** A. Employment/Salary (full or part-time):; University of Arizona. Other; NeuTherapeutics, LLC. **F. Vitali:** A. Employment/Salary (full or part-time):; University of Arizona.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.06/C67

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

Support: Ressler Family Foundation

Title: Cell-type specific transcriptomics reveal early gliovascular dysfunction in a mouse model of tauopathy

Authors: *Y. KOMURO, S. CARMICHAEL, J. D. HINMAN;
Neurol., UCLA, Los Angeles, CA

Abstract: Cerebrovascular abnormalities have long been recognized as contributors to vascular dementia and are increasingly implicated in the pathogenesis of Alzheimer's disease and related tauopathies. However, the specific involvement of tau-mediated pathways in vascular dysfunction remains poorly understood. To address this gap, we developed a cell-type specific viral approach for transcriptional profiling using RiboTAG, aimed at identifying novel molecular pathways within the multicellular environment of the neurovascular unit (NVU) in tauopathy. Viral constructs using cell-type specific promoters (hSynapsin, GFAP, or PDGFRβ) to drive expression of antigen-tagged ribosomes (TRAP) were used to study variance in spatial and temporal gene expression patterns in NVU cell types in the P301S mouse model of tauopathy both prior to and during widespread blood-brain barrier disruption. By coupling vTRAP with endothelial MACS-Seq in P301S transgenic mice, we generated multiple cell-type specific transcriptomic databases of the NVU across several pathologically-relevant time points preceding BBB disruption. Gene ontology analysis indicates that gliovascular cells express multiple molecular programs driving neuronal differentiation, neurite outgrowth, and synaptogenesis in early pathological stages, while later pathological stages show a predominant neuronal response with diminished gliovascular contributions. This specific and temporally

regulated coordination of pathways in astrocytes and pericytes to support neurons injured by tau pathology lessens with age and physiological stress, resulting in active gliovascular dysfunction and cascading neuronal injury. Our findings suggest a paradigm for attenuating gliovascular dysfunction to rescue tau-mediated neurodegeneration. Furthermore, these data implicate novel perivascular molecular pathways in the early pathogenesis of Alzheimer's disease and related tauopathies. Importantly, our analysis reveals alterations in the expression of ligand-receptor pairs involved in intercellular communication between neurons and gliovascular cells, offering insights into potential therapeutic targets for modulating neurovascular dysfunction in tauopathies.

Disclosures: Y. Komuro: None. **S. Carmichael:** None. **J.D. Hinman:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.07/C68

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

Support: PEW Charitable Trust
Cure of Alzheimer's Fund
Owens Family Foundation

Title: Neuronal gene expression regulation by tau oligomers

Authors: *G. EASTMAN[1], R. S. FORT[2], G. S. BLOOM[3];
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Abstract: In early, pre-symptomatic stages of Alzheimer's disease (AD) toxic tau oligomers (TauOs) accumulate in the brain and propagate from neuron to neuron by a prion-like mechanism. Previously, our lab reported that extracellular TauOs (xcTauOs) damage neurons by deforming their nuclei, impairing nuclear-cytoplasmic transport, and altering gene expression by mechanisms dependent on intracellular tau [Sun X. et al Alzheimer's & Dementia, 2023; doi: 10.1002/alz.13535]. However, that study did not address the full extent of gene expression changes caused by xcTauOs. In light of this background, we studied the impact of xcTauOs on gene expression by RNA-seq of human iPSC-derived neurons. For this, cells were challenged with xcTauOs for 24 hours, after which total RNA was collected and analyzed by RNA-seq. Gene expression quantification revealed a moderate global response of differentially expressed genes, using a cutoff of $p<0.05$ and a fold change >1.5. Down-regulated genes were associated with several gene ontology categories, including neurotransmitter activity, ion channels, GABA receptor activity and synapses, among others. In contrast, up-regulated genes were less functionally associated and did not fall neatly into any gene ontology groups. We then used gene

set enrichment analysis to explore the entire neuronal transcriptome response to xcTauOs. In line with the previous result, neurotransmitter receptor activity, potassium channels and synapse-associated genes were down-regulated. However, we also found gene data sets associated with protein synthesis and rRNA processing to be down-regulated after xcTauO exposure. We then explored global levels of protein synthesis by the SUnSET assay and confirmed a net decrease in protein synthesis after xcTauO treatment. To summarize, we observed a whole neuronal transcriptome response to xcTauOs that revealed suppression of numerous genes that control neuron-related functions, as well as an intriguing reduction of total protein synthesis. Thus, xcTauOs appear to have an overall negative impact on both transcription and translation in neurons.

Disclosures: G. Eastman: None. **R.S. Fort:** None. **G.S. Bloom:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.08/C69

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

Title: An Emerging Role for H2A.Z in Alzheimer's Disease

Authors: *J. LUO[1], S. CREIGHTON[2], L. HATEGAN[4], T. MCLEAN[5], B. J. WALTERS[3], I. B. ZOVKIC[2];
[1]Cell & Systems Biol., [2]Psychology, [3]Biol., Univ. of Toronto Mississauga, Mississauga, ON, Canada; [4]Univ. of Toronto, Mississauga, ON, Canada; [5]Dept. of Cell and Systems Biology, Univ. of Toronto, Toronto, ON.

Abstract: Alzheimer's Disease (AD) is a debilitating neurodegenerative disorder affecting 50 million people worldwide, but effective treatments are lacking. We recently identified the histone variant H2A.Z as an epigenetic memory suppressor whose levels increase in the aging mouse hippocampus, generating the hypothesis that aberrant H2A.Z accumulation may promote memory decline in AD. Consistent with this hypothesis, we found that expression for *H2AFZ*, a gene encoding H2A.Z, is elevated in the post-mortem hippocampus of female, but not male AD patients. We confirmed that a similar sex difference occurs in 5xFAD mouse model of AD, whereby female 5xFAD mice accumulate H2A.Z in chromatin to a much greater extent than male mice. To test the functional relevance of this accumulation, we depleted *H2afz* in area CA1 of the hippocampus at 2.5 months of age and tested their object location memory monthly until 8 months of age. *H2afz* depletion enhanced memory only in female mice at every age tested, suggesting that *H2afz* depletion has sex-specific benefits for AD-related memory decline. Enhanced memory was associated with an altered transcriptional profiled and reduced levels of AD pathology markers, including amyloid beta 42 and phosphorylated tau 217. Overall, this study is the first to show that histone variants are implicated in AD and that their function in disease progression and memory is sex specific.

Disclosures: J. Luo: None. **S. Creighton:** None. **L. Hategan:** None. **T. McLean:** None. **B.J. Walters:** None. **I.B. Zovkic:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.09/C70

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

Support: NIH R01 AG073826

Title: Multi-study transcriptomic analysis of Alzheimer's brain tissue: insights and caveats

Authors: F. K. TSURUKAWA[1], N. KHANNA[2,3,4], R. PAL[1], *J. J. LAWRENCE[5,6,4,7];
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Abstract: The majority of existing studies on Alzheimer's Disease (AD) transcriptomic data consider differential expression-based analysis, which are univariate by design and often miss the multivariate nature of genetic interactions, neglecting the potential importance of non-differentially expressed genes in classification tasks.Several existing studies report analyses of single datasets but results are often not replicated in other datasets. Our explorative study is based on three datasets, all of which are transcriptomic analyses sampled from postmortem human brain tissue, comparing neuropathologically diagnosed AD cases with control patients with normal cognitive and functional diagnostic.Our methods include feature selection to narrow down the set of potential genes followed by performance evaluation of gene subsets to identify genes associated with AD in a multivariate modeling approach.Through our methods, several genes are implicated in AD without being significantly differentially expressed, such as RLBP1, BRINP3, C17orf58, TRIB1 and SHISA4. Moreover, genes SCG3, CLK4, STARD7 and WNT7B are only able to obtain 70% accuracy scores in a univariate approach but display consistent performance when paired with other genes when evaluated across all three datasets.Our research suggests that both KCNIP1 and SLC38A2 may be involved in AD through a previously unexplored mechanism. KCNIP1, nominated in Agora in 2018, may be involved in AD pathophysiology through its interactions with calcium signaling pathways and trafficking of potassium channels, which are critical for maintaining neuronal function and integrity, while SLC38A2 encodes a sodium-coupled neutral amino acid transporter and is implicated in amino acid metabolism and neurotransmitter synthesis. We observe several epigenetic associations with AD. As far as we know, those genetic associations are not yet documented in publications. Our goal is to emphasize the integration of machine learning techniques beyond traditional gene differential expression analyses and report the caveats of using specific datasets from different

studies. We designed a machine learning based pipeline and present the gained insights from the multi-study multivariate analysis of three datasets along with the caveats of such analysis and the recommendations to follow.

Disclosures: F.K. Tsurukawa: None. **N. Khanna:** None. **R. Pal:** None. **J.J. Lawrence:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.10/C71

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

Support: Aligning Science Across Parkinson's (ASAP)

Title: Investigation of age-related transcriptional alterations in the basal forebrain of a model of Alzheimer's Disease in Down Syndrome

Authors: *A. JOHNSTONE[1], W. C. MOBLEY[2];
[1]UCSD, San Diego, CA; [2]Dept. of Neurosciences, Univ. of California San Diego Dept. of Neurosciences, La Jolla, CA

Abstract: The basal forebrain provides major cholinergic, glutamatergic and GABAergic innervation to the cortex and hippocampus, and regulates critical and diverse processes such as attention, wakefulness, and memory and learning. People with Down Syndrome are at extreme risk of developing Alzheimer's disease due to an extra allele of amyloid precursor protein (APP) on chromosome 21, during which the basal forebrain is particularly vulnerable to neurodegeneration. In mice, Alzheimer's Disease in Down Syndrome is modeled in the Dp16 line by duplication of a region of mouse chromosome 16 with substantial homology to human chromosome 21, resulting in 113 trisomic genes. Here, we utilized single nucleus RNAseq and ATACseq to investigate transcriptional alterations within neuronal and non-neuronal populations of the basal forebrain of young (3-5 months) and ages (14-16 months). By differential gene analysis, we identified alterations in many glutamatergic and GABAergic populations, and cholinergic neurons, in young and old Dp16 versus 2N euploid controls. Among these alterations are components of machinery regulating synaptic transmission, plasticity, and energy metabolism. We also found activation of transposable elements in neurons and non-neurons in aged Dp16, relative to young Dp16 and young 2N controls, indicating derepression of regions of chromatin with disease and age. We found that trisomic genes were heterogenously transcribed across cell types, indicating that some types may be more vulnerable to the downstream effects of trisomic genes than others. Notably, microglial transcription was dysregulated in both young and old Dp16 relative to 2N controls. Markers of homeostatic microglia are elevated in young Dp16 versus young 2N controls, but depleted in young Dp16 versus aged 2N controls. Markers of cytokine response and interferon response microglia are elevated and dysregulated at both young and old time points, suggesting activation of neuroinflammatory programs, and no clear

disease associated microglia phenotype was observed. Ongoing work aims to understand the consequences of these altered states. Taken together, these findings indicate alterations in transcriptional programs in the basal forebrain in a model of DS-AD, and an interaction between trisomy and aging in Down Syndrome.

Disclosures: A. Johnstone: None. **W.C. Mobley:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.11/C72

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

Support: R01AG047928
R01AG053987
RF1AG064909
RF1AG068581

Title: Mouse models of Alzheimer's disease with U1 snRNP splicing dysfunction

Authors: *P.-C. CHEN[1], X. HAN[2], K. E. HARPER[3], Y. JIAO[4], J. PENG[5];
[1]St Jude Children Res. Hosp., Memphis, TN; [2]St Jude Children's Res. Hosp., Memphis, TN; [4]Structure biology, [5]Structural Biol., [3]St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Proteinopathies are the hallmark of Alzheimer's disease (AD) which is the most common cause of dementia and neurodegenerative disease. It is characterized by the pathologies of Aβ plaques and Tau neurofibrillary tangles. However, recent proteomics profiling has revealed another significant feature: aggregation of the components of U1 snRNP complex in AD, specifically U1-70K and its N-terminal truncated form (N40K). Recently, we have proved that N40K, in addition to its propensity for detergent insolubility, exerts a dominant negative effect which results in loss of U1-70K levels, and mRNA splicing impairment in primary neurons. N40K transgenic mouse model (N40K-Tg) shows aberrant splicing events, neuron loss, synaptic dysfunction, and cognitive impairment. Crossing of N40K-Tg and the 5xFAD amyloidosis mice generates mouse model displaying both splicing impairment and Aβ plaques pathology. Analysis on this model indicates RNA splicing defect synergizes with the amyloid cascade to remodel the brain transcriptome and proteome, deregulate synaptic proteins and accelerate cognitive decline. Here we report two new N40K mouse models. (1) Tetracycline-inducible mice: We generate moPrp.TRE3G-N40K line and cross with CaMKIIα-tTA mice. The N40K Tet-Off mouse model displays prominent neurodegeneration. (2) N40K.Tau double Tg mice: Crossing N40K-Tg with Tau P301S mice generates model with Tau tangles and loss of U1-70K pathology. With these novel animal models, we can further unravel the etiology of dysfunctional U1 snRNP and its synergetic effects with Aβ plaques or Tau tangles in AD.

Disclosures: P. Chen: None. **X. Han:** None. **K.E. Harper:** None. **Y. Jiao:** None. **J. Peng:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.12/C73

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

Title: Neurovascular gene co-expression networks in brain aging and tauopathy

Authors: *S. SEOL, Y. KOMURO, J. D. HINMAN;
Neurol., UCLA, Los Angeles, CA

Abstract: Alzheimer's disease (AD) is a leading cause of neurologic disability and death. Although it is an age-related neurodegenerative disease, the biological mechanisms of aging related to AD are not well understood. Recently, the link between dysfunction of the neurovascular unit and AD is recognized in both disease models and AD patients. Here we used the tau transgenic PS19 mouse to delineate the influence of mutant tau in aging-related neurovascular pathology of AD. RNAs from the cells of the neurovascular unit in frontal cortices of 6-month-old and 9-month-old PS19 transgenic and littermate control mice are separated by cell types using viral translating ribosome affinity purification (TRAP) technology. Cell type-specific translating mRNAs from neurons, astrocytes, and pericytes were sequenced and resulting transcriptomes analyzed by multiWGCNA to reveal the differences in gene co-expression networks by age and genotype. Five networks were constructed: combined network, 6-month-old network, 9-month-old network, PS19 network, and wild type network. To elucidate the role of the vascular system in AD pathology, we selected and further analyzed a pericyte gene co-expression module, of which eigengenes are positively correlated with pericyte ($r > 0.3$, $p < 0.05$). The most AD-related pericyte module in combined network, COM7, consists of 300 genes. Expression of COM7 genes were increased in pericytes of 9-month-old wild-type mice than 6-month-old wild-type mice, but expression was reduced in PS19 mouse cortices. This gene module was preserved in other networks, but not in 6-month-old network. Gene ontology of COM7 indicates it is related to mRNA destabilization and transcription factor activity. We used the connectivity map (CMap) database to find genetic and small molecule modulators for this module which points to several novel gene candidates that may influence neurovascular dysfunction in AD. Future studies will focus on refinement of neurovascular gene co-expression networks across age, genotype, and cell type and determine the molecular mechanisms which contribute to dysfunction of the neurovascular unit in tauopathy. Understanding the key mechanisms of aging in AD is expected to contribute to the development of new treatments for AD and preserve neurovascular function with age.

Disclosures: S. Seol: None. **Y. Komuro:** None. **J.D. Hinman:** None.

Poster

PSTR447: Alzheimer's Disease: Genomics and Other Omics Approaches III

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR447.13/C74

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

Support: R01NS104117
R01NS109221

Title: Elovanoids (ELV-N32 and ELV-N34) promote neuroprotection, modulate tau hyperphosphorylation, neuronal integrity in a cellular model of Alzheimer's disease.

Authors: *S. BHATTACHARJEE[1], N. G. BAZAN[2];
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Abstract: Elovanoids (ELVs) are cell-specific neuroprotective lipid mediators derived from 32:6n3 and 34:6n3 that contribute to neuronal and photoreceptor cell integrity and survival. ELVs have shown neuroprotection in also *in vivo* models of cerebral ischemia (Jun et al, 2017. Sci Rep 7(1):5279). Epigenomic perturbations are linked to telomerase integrity and histone modifications, which are mediated by inflammatory responses, senescence, and aging. Given that ELVs protect neuronal-glial cells, RPE cells and photoreceptors, we hypothesized that ELVs may act as epigenetic regulators by counteracting the damage triggered by several stressors in primary human neuronal-glial cells. The purpose of this work was to find out how ELVs may act as epigenetic modifiers. Serum-starved primary human neuronal-glial cultures were exposed to uncompensated oxidative stress (UOS) [H_2O_2 (1200μM)+TNFα(10ng/ml)] or oligomeric amyloid beta (Oaβ) (10μM) or erastin stressed (10μM) (perturbs ferroptosis-dependent cell death) and treated with ELVs (200nM). RNA transcripts analyzed by RT-PCR for telomerase integrity and telomere length, senescence gene programming; DNA and histone modifications assayed by ELISA. In neuronal glial cells, ELVs counteract UOS or Oaβ DNA methylation 5-methyl cytosine (5-mC) perturbation, ten-eleven translocation (TET)/DNA hydroxymethylation (5-hmC), DNA methyltransferase (DNMT) activity, and histone modifications (H3K9 hypermethylation and acetylation), thereby restoring telomere length attrition and telomerase activity. ELVs also counteract senescence-associated gene transcription: $p16^{INK4a}$, $p27^{KIP}$, $p21^{CIP1}$, and p^{53}. We uncovered that ELVs regulate epigenetic cues mediated by DNA and histone modifications, promoting neuronal and RPE cell function and protecting neuronal integrity. The work was funded by the NINDS grants R01NS104117 (NGB) and R01NS109221 (NGB).

Disclosures: S. Bhattacharjee: None. **N.G. Bazan:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.01/C75

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

Title: Distinct patterns of cortical thinning associated with cognitive decline in Alzheimer's disease

Authors: *C. HUMPHRIES[1], J. BERO IV[2], S. SARKAR[2], H. LEE[2], D. LEE[3,2];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder affecting older adults that is characterized by progressive cognitive decline. Over the course of the disease, increasing levels of brain atrophy result in widespread loss of neuronal function and deficits in cognition. Previous research suggests that there are several subtypes of the disease that have varying patterns of behavioral decline and regional atrophy. In the current study, we investigated how cognitive deficits in three domains (memory, semantics, and executive function) correlated with regional patterns of brain atrophy in AD. Data from 775 subjects were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which included MRI-based cortical and subcortical brain volumes and neuropsychological scores. A set of 18 sub-scores were chosen from the neuropsychological data and grouped into three categories based on whether the task involved episodic memory, semantics, or executive function. For each group of scores, principal components analysis was used to derive a single score based on the first principal component. A regression analysis was used to test the relationship between the three cognitive scores and regional brain volumes. The Memory score showed significant effects in the bilateral medial temporal lobe, hippocampus, and amygdala, the Semantic score was primarily localized to the left temporal pole, superior, and inferior temporal lobes, and the Executive score correlated with a wide distribution of brain areas in the frontal and parietal lobes. The results align with current models of cognitive function and suggest that there are heterogeneous patterns of brain atrophy in AD that produce different patterns of cognitive decline.

Disclosures: C. Humphries: A. Employment/Salary (full or part-time):; Neurogazer USA. **J. Bero:** A. Employment/Salary (full or part-time):; Neurogazer USA. **S. Sarkar:** A. Employment/Salary (full or part-time):; Neurogazer USA. **H. Lee:** A. Employment/Salary (full or part-time):; Neurogazer USA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer USA. **D. Lee:** A. Employment/Salary (full or part-time):; Neurogazer USA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogazer USA.

Poster

PSTR448: Alzheimer’s Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.02/C76

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

Support: HR21C1003 Korea Health Industry Development Institute (KHIDI)
HI22C0724 Korea Health Industry Development Institute (KHIDI)
HR22C1734 Korea Health Industry Development Institute (KHIDI)
RS-2024-00406876 Korea Health Industry Development Institute (KHIDI)
#6637-303 Korea Disease Control and Prevention Agency

Title: Assessing cognitive impairment and disability in older adults through the lens of whole brain white matter patterns

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Abstract: Introduction: This study investigates the utility of whole brain white matter patterns, derived from advanced multimodal neuroimaging, as novel biomarkers for assessing cognitive impairment and disability in older adults presenting with cognitive complaints. These patterns represent an innovative approach to understanding the structural connectivity that may be disrupted in various stages of neurodegenerative diseases.
Methods: We conducted a comprehensive analysis of magnetic resonance imaging (MRI) and amyloid positron emission tomography (PET) scans, alongside blood-based biomarkers for Alzheimer's disease (AD), in a BICWALZS cohort of 454 participants. The study focused on the variability of white matter patterns across individuals (WM-ISV) and their correlation with established clinical biomarkers, providing insights into the underlying mechanisms of disease progression.
Results: The demographic analysis of participants revealed significant differences in age, genetic markers, and biomarker profiles across various stages of neurodegenerative diseases. Notably, patients with AD showed a higher prevalence of the APOE ε4 allele and elevated levels of specific neurodegenerative biomarkers such as neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau protein (pTau217). Our ensemble model, integrating data from MRI and amyloid PET scans, achieved a classification accuracy of 88.3% ± 1.5% for cognitive impairment and 77.8% ± 2.0% for functional disability, significantly surpassing the performance of models using single imaging modalities. Crucially, WM-ISV was found to correlate significantly with these blood-based biomarkers, indicating its potential relevance in the pathophysiology of neurodegenerative disorders.
Discussion: The integration of WM-ISV into neuroimaging analytics significantly enhances diagnostic accuracy and correlates strongly with key biomarkers of neurodegeneration. This finding underscores the potential of white matter pattern analysis as a valuable tool in clinical settings, aiding in the diagnosis and management of cognitive disorders. By providing a more nuanced understanding of brain structure-function relationships, this approach could significantly refine diagnostic and therapeutic strategies, ultimately improving patient outcomes in neurodegenerative diseases.

Disclosures: H. Roh: None. **D. Park:** None. **S. Son:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.03/C77

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

Support: NSF NeuroNex

Title: Ultrastructural Changes in Synapses and Mitochondria in Mouse Models of Alzhiemer's Exposed to Intermittent Hypoxia

Authors: *A. HARSHAW[1], A. M. SOROKINA[1], V. SAMPATHKUMAR[1], H. GAN[1], S. SISODIA[2], A. J. GARCIA, III[3], N. B. KASTHURI[1];
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Abstract: Alzheimer's disease (AD) and sleep apnea (SA) affect millions worldwide, characterized by impairments in memory, mood, and coordination. Notably, individuals with SA are at an elevated risk of developing AD, yet the underlying mechanisms linking these disorders remain incompletely understood. Part of the problem was that until recently, it was hard to image brains at the nanoscale over large volumes. We address that gap and use large-volume serial electron microscopy and synchrotron source X-ray microscopy to investigate synaptic and mitochondrial changes in transgenic mouse models of AD in a mouse model of sleep apnea (Intermittent Hypoxia - IH). Specifically, amyloid beta transgenic animals (CeAPP-PS1) were exposed to 7 days of IH (8 hours/day) and then prepared for large-volume EM and X-ray imaging.We find a twofold increase in the number of amyloid plaques in IH-exposed adult transgenic mice (between 7 and 9 months of age), in the cortex and hippocampus, compared to AD-alone animals. However, paradoxically, CA1 pyramidal neurons in IH-exposed transgenic mice showed a 20-40% increase in synaptic density in proximal and distal dendrites, relative to animals with AD alone. Moreover, mitochondria were notably longer (four- to eight-fold) under IH conditions, suggesting increased mitochondrial fusion. Leveraging automated segmentation of electron microscopy datasets, we aim to track thousands of mitochondria across experimental conditions and explore their distribution within and outside of dystrophic plaques and in different cell types, e.g., vascular cells. We conclude that IH increases plaques, mitochondrial lengths, and, surprisingly, increases synapse number in the context of AD. We further conclude that large-scale investigations into hippocampal ultrastructure are warranted to elucidate additional insights into AD pathogenesis.

Disclosures: A. harshaw: None. **A.M. Sorokina:** Other; Argonne National Laboratory, Lemont, IL. **V. Sampathkumar:** Other; Argonne National Laboratory, Lemont, IL. **H. Gan:** None. **S. Sisodia:** None. **A.J. Garcia:** None. **N.B. Kasthuri:** Other; Argonne National Laboratory, Lemont, IL.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.04/C78

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

Support: R01 NS074980
RF1 MH126732
RF1 MH128875
UM1 NS132173

Title: A BrainSuite pipeline for quantifying neuroanatomical variation over time

Authors: *S. FANG[1], Y. KIM[1], A. A. JOSHI[4], D. W. SHATTUCK[2], D. J. TWARD[3];
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Abstract: Quantifying variability in anatomical form is critical to understanding growth, aging, or neurodegeneration. The latter is recognized as a biomarker for Alzheimer's disease (AD), but challenges remain before it can be used clinically. In this work we addressed the challenge of quantifying neurodegeneration by designing a new computational pipeline to analyze neuroimaging data over time. It inputs triangulated surfaces contouring brain structures and their acquisition times; it outputs thickness and surface area change at each vertex or face of the surface; and it computes statistical significance with familywise error rate control.
Our pipeline operates on the cortical surface mesh outputs of BrainSuite. It performs geodesic regression in the space of diffeomorphisms - spatial warpings that can be used to study shape change. Geodesic regression generalizes least squares linear regression to spaces where "linear" is described using a metric tensor at every point. Here the metric is defined using Large Deformation Diffeomorphic Metric Mapping, which provides a mathematical description of the metric space of shape changes. This regression model filters out inconsistent sources of variability over time while preserving overall trends.
We register sets of surfaces with an optimal diffeomorphism, which leads to a minimization problem over regularization and matching terms. From a given atlas template, we jointly estimate a sequence of diffeomorphic transformations by gradient descent: (i) a deformation to a subject specific template; (ii) a time dependent deformation through the time series of observations; (iii) residual deformations connecting the time series to each observation; and (iv) a rigid transformation describing any differences in pose. The sequence of transformations provides an alignment between our atlas template and each observation. By following deformation (ii), we can estimate changes to thickness and surface area without referring to sources of variability explained by (iii) and (iv).
We applied our pipeline to a set of T1-weighted MRI from OASIS-3 (15 AD, 73 control, 2-6 images each over up to 12.1 years), whose entorhinal cortex surfaces were generated using the BrainSuite BIDS App and a custom atlas. We computed the optimal deformation for patient samples and measured cortical thickness and surface area change. We used a mixed-effects

model and showed statistically significant results that differentiated patients with Alzheimer's disease from the control group. Family-wise error rate was controlled using permutation testing. In the future, this pipeline will be made available as part of the BrainSuite software package.

Disclosures: S. Fang: A. Employment/Salary (full or part-time):; UCLA. **Y. Kim:** A. Employment/Salary (full or part-time):; UCLA. **D.W. Shattuck:** A. Employment/Salary (full or part-time):; UCLA. **D.J. Tward:** A. Employment/Salary (full or part-time):; UCLA.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.05/C79

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

Support: FWO-G045420N
SAO-FRA 2020/027

Title: Resting-state network dynamics alterations, memory impairments and their relationship in the TgF344-AD model of Alzheimer's disease.

Authors: A. AL-AWLAQI, L. BERCKMANS, S. DE WAEGENAERE, I. VAN SPILBEECK, M. VERHOYE, ***M. H. ADHIKARI**;
Biomed. Sci., Univ. of Antwerp, Antwerp, Belgium

Abstract: Resting-state (RS) fMRI studies of Alzheimer's disease (AD) impact on brain function commonly use functional connectivity (FC) ignoring short-timescale network dynamics captured by co-activation patterns (CAPs) that are accurate at classifying transgenic rodents of AD from healthy controls. Here, we analyze high temporal resolution RS-fMRI data using FC and CAPs to evaluate AD's functional impact at pre-plaque and plaque stages in the TgF344-AD rat model and investigate their relationship with memory impairments and markers of AD pathology in blood plasma at the plaque stage. We acquired RS-fMRI data ((9.4T Bruker Biospec, TR 0.6s, 1000 GE-EPI volumes) in TgF344-AD (TG) and wildtype (WT) male rats (N=15 per group), under anesthesia, at 4 (pre-plaque) and 10 (plaque stage) months of age. We calculated region of interest (ROI), and network-level FC from preprocessed RS-fMRI images. We obtained CAPs by clustering concatenated preprocessed volumes of all subjects at both time points into 2-20 clusters, using spatial correlation distance, identifying the optimal number of clusters, and taking a voxel-wise average across all volumes with identical cluster membership. Group and age effects on FC, and CAP spatial and temporal properties were assessed using repeated measures ANOVA. After the 10-month scans, we (a) collected blood samples to measure levels of $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, phosphorylated Tau, and (b) assessed working and reference memory using a radial arm maze (RAM) for 10 days (acquisition period) after a 5-to-7-days-long habituation period. While WT rats improved their working memory over time, TG rats did not; they also committed significantly more reference memory errors than WT rats. Lateral cortical

network (LCN) FC was significantly higher in the TG ($p < 0.05$, FDR corrected) rats only at the plaque stage and correlated with a higher percentage of time spent in incorrect arms reflecting reference memory deficits. Among the six CAPs we obtained, TG rats at the pre-plaque stage showed hyperactivation in the default mode-like network (DMLN) regions and hippocampus in one CAP and the cingulate cortex in another. At the plaque stage, TG rats showed lower activations, especially in the DMLN, across multiple CAPs. DMLN hyperactivation at the pre-plaque stage is in line with electrophysiology and memory-encoding task-fMRI studies' finding of hippocampal hyperactivation and reduced inactivation of the DMLN preceding the plaque formation in animal and cell models. Our findings demonstrate that RS-FC changes at the plaque stage correlate with memory deficits while changes in RS functional dynamics can tease out early signatures of AD in a translational rat model.

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Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.06/C80

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

Support: RF1 AG071805
U01 AG032969
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R56 AG072599
R01 AG067598
R01 AG074004
R01 AG067598
P30 CA008748
U54 OD020355
R24 CA83084
A2022020F

Title: Epichaperome imaging PET probes for precision medicine in Alzheimer's disease

Authors: *S. SHARMA[1], V. JALLINOJA[1], C. DIGWAL[1], A. RODINA[1], P. PANCHAL[1], S. BAY[1], T. ROYCHOWDHURY[1], S. D. GINSBERG[2], M. ISHII[3], R. CARSON[4], P. ZANZONICO[1], N. PILLARSETTY[1], G. CHIOSIS[1];
[1]Mem. Sloan Kettering Cancer Ctr., New York, NY; [2]Nathan Kline Inst., Orangeburg, NY; [3]Weill Cornell Med., Dallas, NY; [4]Yale Sch. of Med., New Haven, CT

Abstract: Alzheimer's disease (AD) represents a complex interplay of genetic, epigenetic, and environmental factors, leading to alterations in brain circuitry and cognitive decline. Despite

extensive research, identifying effective therapeutic targets to halt AD progression remains a significant challenge due to the involvement of multiple pathological pathways. Our recent investigations have unveiled a novel aspect of AD pathology: the impact of stressors associated with the disease on protein-protein interaction networks through specialized structures known as epichaperomes. These long-lived formations, unique to afflicted cells, consist of chaperones and other components, disrupting proper protein interactions and impairing neuronal and brain function. Epichaperomes exacerbate perturbations in molecular interactions within affected cells, contributing to AD-associated biological dysfunctions. Notably, the ability of epichaperome disruptors to reverse AD-related phenotypes underscores their crucial role in modulating functions underlying disease pathology, offering a promising avenue for therapeutic intervention. In this study, we elucidate our endeavors in designing, synthesizing, and characterizing small molecule epichaperome imaging probes. Through a comprehensive array of biochemical and functional assays, conducted both in vitro and in vivo, including investigations on murine models and human subjects, we demonstrate how these small molecules can selectively and kinetically distinguish the small fraction of epichaperomes from the abundant chaperone pools present throughout the body. Utilizing proof-of-principle evidence from mouse models, we showcase how an epichaperome imaging probe can unveil the region- and age-dependent formation of epichaperomes in disease-relevant areas. Additionally, we present the outcomes of a pilot feasibility clinical study, illustrating the imaging and quantification of epichaperomes in human patients using PET scans. In conclusion, epichaperome imaging tools offer substantial diagnostic potential in AD. When integrated with anatomical and other neuroimaging techniques, alongside plasma biomarkers, these tools can facilitate the diagnosis and quantification of molecular changes underlying functional decline in the AD brain, even prior to the onset of tau and amyloid pathology. Furthermore, they hold promise as companion diagnostics in the development of epichaperome-targeting drugs, aiding in patient selection, real-time monitoring of target engagement by epichaperome disruptors, and quantitative assessments to optimize dose and treatment regimens.

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Poster

PSTR448: Alzheimer’s Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.07/C81

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

Support: R01AG080468

Title: The Effects of Bilingualism on Cognitive and Neural Reserve in Cognitive Impairment

Authors: *Z. BATY[1], M. ROSSELLI[2], M. LANG[2], S. COOMBES[1];
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Abstract: Bilingualism may contribute to cognitive reserve, and neural reserve, protect against cognitive decline, and delay the onset of dementia. The evidence is mixed, however, with retrospective studies more likely to show effects, whereas prospective studies do not. Education and cultural differences may account for differences between studies, limiting the convergence of prior studies. We directly address these limitations in the current study by assessing the effects of bilingualisms on cognitive reserve and brain reserve in cohorts of 371 individuals including bilinguals (Spanish/English speakers; *n* = 150) and monolinguals [Spanish: (*n* = 74),; English: (*n* = 147)] with normal cognition (*n* = 100), MCI (*n* = 218), and Dementia (*n* = 53,). Diagnosis was determined using the clinical dementia rating scale (CDR). Bilingualism was assessed using the Language Efficiency and Proficiency Questionnaire (LEAPQ). All participants also completed a comprehensive battery of cognitive tests (MMSE, MoCA, HVLR, WMS-IV, and LASSI-L), as well as a T1-weighted MRI scan. The T1 scan was processed using Freesurfer to segment and parcellate CSF/gray/white matter and derive region specific measures of volume and cortical thickness, from which the McEvoy and Schwarz signatures were then calculated. The Schwarz signature calculated as the mean thickness of 6 Alzheimer's Braak regions. The McEvoy signature is calculated as the sum of weighted residuals of thickness or volume corrected for age, sex, and intracranial volumes for a group of regions associated with MCI. Language (bilingual, monolingual) by Clinical Diagnosis (normal cognition, MCI, and dementia) ANCOVAs were run for cognitive tests and the McEvoy and Schwarts signatures, controlling for appropriate covariates (age, sex, education, and APOE ε4 status). Although strong effects of Diagnosis were evident across all cognitive and brain measures in the expected directions, no significant Language or Language by Diagnosis interactions were found. Our observations, in a culturally matched sample of bilingual and monolingual English/Spanish speakers, suggest that the Schwarz and McEvoy signatures are not sensitive to bilingualism, and that better matching of culture across Language Groups may diminish associations between bilingualism and cognitive reserve.

Disclosures: Z. Baty: None. **M. Rosselli:** None. **M. Lang:** None. **S. Coombes:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

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Program #/Poster #: PSTR448.08/C82

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

Support: 1R01AG053961 (NIH/NIA)

Title: Among Older African Americans, High-Risk ABCA7-80 Allele Carriers Have Lower Medial Temporal Lobe Dynamic Network Flexibility than APOE-ε4 Allele Carriers

Authors: *M. BUDAK[1,2], B. FAUSTO[3], W. PIASZCZYNSKA[3], P. WHITE[3], M. A. GLUCK[3]; [1]Rutgers Univ. Newark, Newark, NJ; [2]Center for Molecular and Behavioral Neuroscience, Rutgers University-Newark, Newark, NJ; [3]Ctr. for Mol. and Behavioral Neurosci., Rutgers University-Newark, Newark, NJ

Abstract: Background: The medial temporal lobe (MTL) is the first region that displays atrophy and neuropathological burden (amyloid plaques and neurofibrillary tangles) during Alzheimer's disease (AD). Although *APOE-ε4* is identified as a well-established genetic risk factor for AD, *ABCA7-80(rs115550680)* is associated with the development of late-onset AD among African Americans. However, the comparative influence of *APOE-ε4* and *ABCA7-80* on MTL structure and neural functions among African Americans is not yet known. The present study investigated the effect of *APOE-ε4* and *ABCA7-80* high-risk alleles on the volumetry and dynamic network flexibility within the MTL region among cognitively healthy older African Americans.**Methods:** 143 older, cognitively healthy African Americans drawn from the ongoing longitudinal study, *Pathways to Healthy Aging in African Americans* completed saliva collection for genotyping and underwent a neuroimaging session. Hippocampal subfield and MTL region volumetry and MTL dynamic network flexibility, as well as genetic risk (high-risk versus non-risk) conferred by *APOE-ε4* and *ABCA7-80,* were calculated for each participant.**Results:** While there was no difference in MTL region volumetry ($p>0.005$), trend-level differences were found in MTL dynamic network flexibility between high-risk and non-risk allele carriers for ABCA7-80 ($F=3.531$, $\eta^2=0.025$, $p=0.062$) and APOE-ε4 allele ($F=2.421$, $\eta^2=0.017$, $p=0.122$). Individuals with the *ABCA7-80* high-risk allele exhibited significantly lower MTL dynamic network flexibility compared to those with the *APOE-ε4* allele (*$F=4.577$, $\eta^2=0.067$, $p=0.036$*) and had no difference in volumetry (*$p>0.005$*).**Conclusion:** As compared to *APOE-ε4,* the *ABCA7-80* high-risk allele may better capture the dynamic neural dysfunction in the MTL network among cognitively healthy older African Americans.

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Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

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Program #/Poster #: PSTR448.09/C83

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

Support: National Institutes of Health (NIH) R00MH120053 (BRAIN Initiative)
McDonnell Center for Systems Neuroscience, Washington University St. Louis Medical School
McDonnell Center for Cellular and Molecular Neurobiology, Washington University St. Louis Medical School

Title: In-vivo non-invasive imaging of neurovascular dynamics in retina: implications for detection and monitoring of neurodegenerative diseases

Authors: *K. M. DUNCAN[1], M. DAGNACHEW[2], Z. HUSAIN[3,4], I. SENCAN-EGILMEZ[5]; [1]Mallinckrodt Inst. of Radiology, Biophotonics Res. Ctr., Washington Univ. in St. Louis Med. Sch., St. Louis, MO; [2]Mallinckrodt Inst. of Radiology, Biophotonics Res. Ctr., [3]Mallinckrodt Inst. of Radiology, [4]Radiology, Washington Univ. in St. Louis, St. Louis, MO; [5]Mallinckrodt Inst. of Radiology, Biophotonics Res. Ctr., Washington Univ. St. Louis Med. Sch., St. Louis, MO

Abstract: Understanding the processes of disease pathology in Alzheimer's and dementia allows accurate and potentially earlier detection and grading, yet the ability to detect AD pathology in vivo prior to obvious symptoms is an elusive one. Since cerebral subcortical white matter often exhibits early pathological developments due to global hypoperfusion, results suggest identifying pathology in retinal microcirculation has untapped potential for biomarker detection in brain diseases, and the ability of noninvasive microscopic imaging to visualize biomarkers has great implications as a neuropathology detection tool.
In vivo microscopic imaging of the mouse retina is a pivotal tool for exploring neurovascular structure and function, particularly in identifying patterns of early neurodegeneration biomarkers. Utilizing two-photon microscopy (2PM) we measure partial oxygen pressure and blood flow non-invasively through the pupil or sclera, providing maps of microvascular morphology, blood flow & oxygenation in microvasculature and surrounding tissue. In addition to age, APOE genotypes are strong AD risk factors; and though APOE2 is protective relative to APOE3, APOE4 is a high risk factor as 65% of patients have at least one copy of the gene. The neurovasculature in the retina of 10 male & female, aging (knock-in APOE2, 3, 4 genotypes) and control (C57/BL6) mice are imaged, showing any differences in sex, genotype, and age. Pathology will be confirmed in vivo/ex vivo with fluorescent or phosphorescent labeled biomarkers. Mice are non-invasively imaged through the pupil and sclera using 2PM to visualize physiological underpinnings of vascular & tissue oxygenation and blood flow distribution. These are quantified on a microscopic scale via MATLAB analysis, and imaged ex vivo supplementing in vivo visualization of neurovascular morphology. In quantifying these neurovascular changes occurring in aging, we underscore the potential of retinal optical imaging techniques as powerful means for early detection and monitoring of neurodegenerative diseases. A retinal imaging approach is currently underutilized despite the potential of these non-invasive techniques in identifying neuropathology, and these methods offer a look forward to non-invasive AD diagnostics and improving understanding of early stage disease mechanisms.

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Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.10/C84

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

Title: Hippocampal CA1 atrophy in individuals with a family history of Alzheimer’s disease

Authors: *M. AL AMIN[1,2], H. KARAHAN[1,2], B. KIM[1,2], J. KIM[1,2,3];
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Abstract: Alzheimer’s disease (AD) is one of the leading causes of cognitive decline and dementia. The trajectory of AD often begins long before the manifestation of dementia symptoms, necessitating the exploration of biomarkers for early detection and intervention. Individuals with a family history of AD (FH-AD) are at a greater risk of developing AD themselves. Neuroimaging studies have demonstrated reduced hippocampal subfields in AD patients. However, our knowledge of hippocampal subfield atrophy in individuals with a FH-AD is limited.To identify hippocampal subfield volumes among individuals with a FH-AD, we examined structural magnetic resonance imaging (MRI) data from PResymptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) and compared the data with those of the Alzheimer's Disease Neuroimaging Initiative (ADNI). We analyzed 41 cognitively unimpaired participants enrolled in the PREVENT-AD cohort with a parental or multiple-sibling history of AD. We compared this cohort with 77 healthy controls (HCs) and 91 patients with mild cognitive impairment (MCI) from the ADNI. Hippocampal subfield volumes were delineated from high-resolution T1-weighted 3T MRI scans obtained at baseline and during a 4-year follow-up period. The longitudinal data were preprocessed with the standard longitudinal FreeSurfer pipeline. We created an unbiased subject-specific template for pre-processing structural image at each time point. This longitudinal approach has demonstrated a decrease in variability within subjects and an enhancement in the ability to identify subtle changes. There was no significant difference in whole hippocampal volume between participants with FH-AD and controls at baseline and follow-ups in both sexes. In males, compared with HCs, FH-AD individuals showed a reduced CA1 volume with age and follow-up. We further quantified the volume of the head anf body portion of the CA1 region. Compared with the controls, male FH-AD individuals showed a significant decrease in the CA1 head but not in the body with age. Similar to CA1, fimbria volume in male FH-AD patients was also decreased compared to those in control subjects with age. In females, we detected significant increases in CA3 and CA4 volumes compared to controls with age and follow-ups. Our results suggest that shrinkage of the hippocampal CA1 region may be used as an early imaging biomarker for male individuals with FH-AD. Taken together, these results may provide valuable insights into detecting disease progression in its early stages and allow for interventions that may slow disease progression or manage symptoms more effectively.

Disclosures: M. Al Amin: None. **H. Karahan:** None. **B. Kim:** None. **J. Kim:** None.

Poster

PSTR448: Alzheimer’s Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.11/C85

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

Support: NIH/NIA U01 grant AG076804
NIH/NIA RF1 grant AG056114
NIH/NIMH BRAIN Initiative U01 grant MH117079

Title: Brainwide Genetic Sparse Labeling, Imaging and Quantitative Analyses of Single-Neuron Morphological Deficits in Mouse Models of Alzheimer's Diseases

Authors: *C. LEE[1,2,3], C. S. PARK[1,2,3], A. J. DE LA ROCHA[1,2,3], M. A. AKRAM[1,3,2], H. Y. CHEN[1,2,3], X. YANG[1,3,4];
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Abstract: The atrophy and loss of dendritic and axonal processes in selective vulnerable neuronal populations is an early and common pathological manifestation of neurodegenerative and neurodevelopmental disorders. It also serves as an important preclinical and clinical readout for developing therapeutics. Despite the importance of neuronal morphologies in understanding the mammalian brain and brain diseases, there is currently a lack of a generalizable systems-biology approach to analyze brainwide single-cell morphologies of genetically-defined mammalian neurons at scale, from labeling and imaging to extraction and quantitative analyses of morphological statistics. MORF3 is a novel mouse model, expressing a tandem Spaghetti Monster reporter protein under two layers of genetic controls, including Cre-dependent activation and stochastic mononucleotide repeat frameshift (MORF), for sparse labeling of genetically defined cell types (Veldman et al., 2020, PMID: 32795398). In this study, we crossed MORF3 mice with 5xFAD mouse model of Alzheimer's disease to sparsely and brightly label the layer 5 Etv1+ cortical pyramidal neurons (L5-PyNs) at 4 and 7 months of age. Dissected brain hemispheres were processed with automated tissue clearing and immunostaining followed by light-sheet imaging of the intact brain hemispheres to obtain high-resolution (0.78μm xyz) datasets for MORF3-labeled neurons. We found that the sparse MORF3 labeling allowed visualization of complete single-cell morphology of Etv1+ L5-PyNs neurons in various cortical regions. Importantly, we discovered dystrophic bulges on the axons, i.e. axonal spheroids, only in labeled L5-PyNs in 4m and 7m 5xFAD brains but not those in wildtype controls. We are implementing a novel pipeline with 3D-Unet (CNN) segmentation model that allow analysis of the entire light sheet dataset for single-neuron morphology and pathology. Our ongoing analyses focus on the distribution of the axonal spheroids and their relationship with cell-intrinsic and external pathologies (e.g. plaques, activated glial cells). Together, our study provides a novel integrated systems biology approach to study brainwide high-resolution mapping of single-neuron morphology and pathology in intact mouse brains.

Disclosures: C. Lee: None. **C.S. Park:** None. **A.J. De La Rocha:** None. **M.A. Akram:** None. **H.Y. Chen:** None. **X. Yang:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.12/C86

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

Support: MH105625
MH124816
MH121069
EB022907
NS086085

Title: Task-dependent latent brain state dynamics predict Alzheimer's pathology

Authors: *Z. GAO[1], L. ZHENG[4], V. MENON[2], W. CAI[3];
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Abstract: Alzheimer’s disease (AD) presents a significant global health challenge, affecting millions worldwide. At the core of AD pathophysiology lies amyloid-β (Aβ) deposition, accompanied by hallmark symptoms of memory loss, and impaired cognitive control. Latent brain states, characterized by dynamic and rapid reconfiguration of neural activation patterns, play a crucial role in supporting cognition. However, disruptions in the persistence and temporal transitions between these brain states may reflect neurophysiological disturbances in AD. This study aims to explore the dynamic interplay of brain states and their implications for memory performance and Aβ deposition using a novel Bayesian Switching Linear Dynamic Systems (BSDS) approach. 121 participants, including healthy elders (63, mean age = 64 years) and individuals with cognitive impairment (52, including 4 AD; mean age = 63 years), underwent a working memory task involving 0-back and 2-back conditions. fMRI data were analyzed using BSDS to identify latent brain states. PET imaging measured Aβ deposition. Healthy controls exhibited higher accuracy in both 0-back and 2-back conditions compared to patients (0-back: 0.73 vs. 0.64, $p = 0.001$; 2-back: 0.71 vs. 0.60, $p < 0.001$). While healthy controls showed faster speed in 0-back than patients ($p = 0.02$), no significant difference was found in 2-back trials ($p = 0.29$). Using BSDS, we identified five latent brain states, denoted as brain states S1 to S5. The Occupancy rate (OC), measuring how often a latent state occurs during the task, and mean lifetime (ML), indicating the dwelling time of a brain state before switching, were used to assess the temporal properties of each latent brain state. Our results revealed that the OC and ML of brain state S3 were negatively correlated with memory accuracy in 0-back trials (OC: $r = -0.27$, $p = 0.01$; ML: S3, $r = -0.22$, $p = 0.046$). Similarly, the OC and ML of brain state S5 were negatively correlated with 2-back memory performance (OC: $r = -0.23$, $p = 0.034$; ML: $r = -0.25$, $p = 0.02$). Furthermore, the OC and ML of brain state S4 during 0-back trials were negatively associated with clinical symptoms of MoCA ($r = -0.38$, $p < 0.001$; $r = -0.31$, $p = 0.004$, respectively). Standardized Uptake Value Ratio measured in ten cortical areas indexed Aβ deposition. Canonical correlation analysis examined the multivariate relation between latent brain states and Aβ deposition, revealing a significant correlation ($r = 0.662$, $p < 0.001$). Our

preliminary data highlight associations between latent brain states, memory performance, and Aβ deposition, underscoring the potential utility of dynamic brain state analysis in elucidating neurodegenerative processes.

Disclosures: Z. Gao: None. **L. Zheng:** None. **V. Menon:** None. **W. Cai:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.13/C87

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

Support: NIH AG069539

Title: Early Diagnosis Of Alzheimer's Disease Using A Novel Nanoparticle-Based Approach: Studies Using The TgF344AD Rat Model

Authors: *A. MURUGAN[1], Y.-J. CHUANG[2], M. AL MANSI[3], A. PALANIYAPPAN[4], S. M. MOHANKUMAR[5], P. S. MOHANKUMAR[6];
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Abstract: Alzheimer's disease (AD) is a chronic neurodegenerative condition that leads to dementia in 60-80% of the affected population. Early diagnosis of this condition can help with the timely initiation of interventional strategies that can delay the progression of this debilitating disease. A noticeable degenerative change occurs in AD patients in a cluster of noradrenergic neurons called the locus coeruleus (LC) neurons 10 years before the onset of clinical symptoms. Being able to identify these neurodegenerative changes non-invasively would be a major breakthrough in AD diagnosis and treatment. However, this has been a challenge since there are no imaging agents that can cross the blood brain barrier (BBB) easily to reach the LC neurons. We have recently developed a nanoparticle that when administered intravenously, can cross the BBB, and target the LC neurons. Their uptake can be monitored using MRI imaging. We aimed to evaluate the nanoparticles' capacity to distinguish the MRI signal intensity in noradrenergic neurons of transgenic AD rats from their age-matched control group within a well-established AD rat model and to examine its longitudinal changes. Middle aged (14-month-old) male and female TgF344AD rats were injected intravenously with the nanoparticle. Animals were anesthetized and imaged in a 7T Varian MRI system at 4, 24 and 48 hours post injection. T2-weighted images were obtained using a fast-spin echo multi-slice (FSEMS) sequence to ensure high resolution and quality. T2 mapping was facilitated by employing a multiple echo multi-shot (MEMS) sequence, enabling the acquisition of quantified MRI images. Qualitative and quantitative analyses of the images were performed using Mango, Adobe Illustrator, Adobe Photoshop, and GraphPad Prism. The results demonstrate that the nanoparticle is capable of crossing the blood brain barrier and reaching noradrenergic neurons by 4 hours with maximum

accumulation occurring at 24 hours in wildtype rats followed by a rapid decline by 48 hours. The accumulation in older TgF344AD rats was markedly reduced compared to their wildtype counterparts ($p<0.05$). Our study highlights the potential of our nanoparticle for diagnosing AD, by demonstrating significant differences in signal intensity in noradrenergic nuclei between wildtype and transgenic rats. The longitudinal analysis underscores the dynamics of nanoparticle distribution post-injection, offering insights into disease progression and diagnostic utility. This pioneering approach not only offers potential diagnostic strategy but also represents a major stride towards addressing the unmet therapeutic needs in AD management.

Disclosures: A. Murugan: None. **Y. Chuang:** None. **M. Al Mansi:** None. **A. Palaniyappan:** None. **S.M. Mohankumar:** None. **P.S. Mohankumar:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.14/C88

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

Support: National Science Foundation Graduate Research Fellowship (FdU)
Ford Foundation National Academies of Sciences, Engineering and Medicine Predoctoral Fellowship (FdU)

Title: Cognitive resilience: The protective influence of the cerebellum in aging and Alzheimer's disease

Authors: *F. D'OLEIRE UQUILLAS[1], E. SEFIK[1], J. SEIDLITZ[2], J. MERRIMAN[1], V. ZHANG[3], M. KISLIN[1], G. J. BROUSSARD[1], A. F. ALEXANDER-BLOCH[4], R. A. BETHLEHEM[5], S. S. WANG[1], J. SEPULCRE[6], P. VANNINI[7], J. GOMEZ[1];
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Abstract: Background: Studying brain reserve — the brain's resilience to age-related change or damage — is crucial for understanding protective mechanisms against cognitive decline. The cerebellum may be a key region in brain reserve, but it has been historically understudied. This investigation delves into this critical area within the largest aging cohort to date. **Methods:** Data were sourced from the Human Connectome Project (n=708, 36-100yrs), UK Biobank (n=45,013, 44-81yrs), and ADNI (n=1,441, 56-95yrs). ADNI participants were cognitively normal, had mild cognitive impairment, or Alzheimer's disease (AD) dementia. We examined associations between cerebellar tissue volume, age, Montreal Cognitive Assessment (MOCA) scores, global PET amyloid burden, and APOE genotype. Statistical models included sex and estimated intracranial volume (eTIV) as covariates, with adjusted household income considered when

available. **Results:** Spatial analysis of HCP-Aging data revealed that aging unfolds heterogeneously across the cerebellum; posterior portions of the cerebellum (Crus I) showed greater effects than anterior regions (Lobule I-III) (Bonferroni-corrected, $p<0.05$). MOCA scores were associated with higher tissue density in the cerebellum ($p<0.0001$), as much as neocortex, and MOCA scores coupled most strongly with posterior cerebellar cortex, overlapping frontoparietal, ventral attention, and default mode network representations. Strikingly, greater volume in this MOCA-related cerebellar cortex signature protected against aging-related cognitive decline ($p=0.029$). We validate tissue aging results in the UK Biobank - again, posterior cerebellum demonstrated the greatest aging effect ($p<0.0001$), and individuals with greater cerebellar volumes showed less decline in processing speed and executive function (Trails Making-B time: $p=0.001$; Digit Symbol Substitution score: $p=0.038$). Across all ADNI diagnostic groups, AD patients with low amyloid- beta burden (Aβ-) exhibited the strongest cerebellar association with MOCA (volume x group, Aβ- AD: $p=0.00004$). In Aβ- individuals, APOE genotype interacted with cerebellar volume on MOCA, with ε4/ε4 carriers showing the greatest effect (volume x APOE, ε4/ε4: $p=0.017$). **Conclusions:** Our large-scale study demonstrates the cerebellum's critical role in mitigating patterns of cognitive decline. This protection persists until significant amyloid burden, and in APOE ε4/ε4 carriers, reshaping our understanding of reserve and AD risk. The cerebellum's integral contribution to brain reserve has substantial implications for aging populations and should be a focus of future clinical research.

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Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.15/C89

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

Title: Region-specific interplay of APOE and cardiovascular risk factors in brain aging: insights from 31,246 UK Biobank participants across age groups

Authors: *Y. GUAN, C. CHENG, B.-B. KOO;
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Abstract: Late-onset Alzheimer's disease (LOAD) is a multifactorial neurodegenerative disease characterized by a complex gene-environmental interaction. Cardiovascular risk factors (CVR) contribute to cognitive decline and may interact with the apolipoprotein-E ε4 (APOE4) allele, a major genetic risk factor of LOAD, to accelerate disease progression. We previously found in a Puerto Rican older adult cohort, that CVR and APOE4 carrier status were associated with reduced brain white matter (WM) microstructural integrity, a well-established early marker for

brain aging (suggesting glial dysfunction and myelin deficits) (Guan *et al.,* 2022, Guan *et al.,* 2023). However, it is unclear whether their effects are 1) brain region-specific, 2) detectable at younger ages or pre-clinical stages of dementia, and 3) generalizable to a larger population. The current study assessed the effects of APOE variants and CVR on WM integrity, hippocampal volume, and cognitive functions from the large-scale, multimodal MRI datasets of UK Biobank (UKB) (N=31,246 White adults without dementia, aged 45-83 years, 53% female), using general linear mixed-effect models adjusting for age, sex, education, and site. Additional modifiable risk factors that may be associated with CVR and brain health, including BMI, waist-hip ratio, smoking, drinking and physical activity were evaluated in age and sex subgroups. Results showed that higher CVR was associated with hippocampal atrophy and a widespread reduction of WM integrity (quantified by lower neurite density with FDR-corrected $P<0.05$) in both middle-aged (45-65y) and older subjects (>65y). The negative impacts of CVR on the hippocampus and nearby WM tracts (i.e., fornix, sagittal stratum, posterior thalamic radiation, etc.) were more pronounced in APOE4 carriers (especially the APOE44 group) than non-carriers. These regions affected by both APOE4 and CVR also correlated with individuals' performance in cognitive domains of memory, executive function, and processing speed. Modifiable risk factors including obesity, central obesity and smoking further moderated the relationship between CVR, APOE, and brain imaging markers, especially in older male participants. In summary, the findings highlight the hippocampus and medial temporal lobe WM as key regions for detecting early effects of APOE4 and CVR on the brain. This comprehensive analysis from the large-scale UKB datasets supports gene-environmental interaction underlying accelerated brain and cognitive aging and emphasizes the necessity to integrate genetic risk and lifestyle-modifiable risk assessments for developing effective prevention and management strategies for LOAD.

Disclosures: Y. Guan: None. **C. Cheng:** None. **B. Koo:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.16/C90

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

Title: Role of the MEN1 gene in cellular and molecular mechanisms underlying Alzheimer's Disease in human autopsied brains

Authors: *Z. KHAN[1], F. IQBAL[2], M. YACOUB[2], A. K. ULFAT[2], N. I. SYED[3];
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Abstract: The Alzheimer's Association reported that 6.9 million Americans aged 65 and older are living with Alzheimer's Disease (AD), thus highlighting the magnitude of this disease burden. The primary targets for drug development in AD have been the pathologically

accumulated amyloid β (Aβ) peptide and tau protein, which form plaques and neurofibrillary tangles, respectively. Despite significant scientific progress, causative pathology in the brain, and the fundamental mechanisms remain elusive. An alternative to the Tau and Aβ narrative is the Cholinergic Hypothesis, which implicates the impaired cholinergic synaptic structures and function in the hippocampus underlying learning, memory and cognition. Menin, a protein encoded by the MEN1 tumor suppressor gene, is involved in synapse formation and synaptic plasticity in the hippocampus whereby it targets and regulates the function of cholinergic receptors underlying learning and memory. Moreover, MEN1 knockdown in a mouse model generates a phenotype analogous to that of AD. We have demonstrated, for the first time, the presence of menin in both the cortex and the hippocampus of post-mortem human AD brains. This study leverages QuPath, an open-source software, to automate the quantification of immunohistochemical markers, overcoming the challenges in large-scale, unbiased quantification, particularly in heterogeneous tissues such as the human brain. This study employs machine learning and pixel classification techniques to quantify alterations in AD-related biomarkers, including synaptophysin, PSD-95, Tau, and menin in human brain tissue. Qualitative and quantitative analysis revealed that PSD-95 expression was notably reduced in AD brain samples which may indicate potential synaptic compromise in AD. Further analysis showed reduced menin expression and synaptic alterations, alongside increased tau expression in AD samples, indicating their potential roles in AD pathology. Additionally, the co-localization of tau and menin in brain tissues from both non-AD and AD samples suggests a potential interaction between these proteins underlying AD pathology. Moreover, a direct molecular and genetic analysis of menin, and its interactions with other proteins (Tau, Aβ) in freshly frozen hippocampal/cortical tissue from human individuals with AD (both early and late onset) and their age-matched controls is warranted. This study takes a novel approach by focusing on the impaired cholinergic synaptic structures and functions in the autopsied human brain tissue thus allowing for direct molecular and genetic analysis, which can provide valuable insights into the mechanisms underlying AD.

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Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.17/C91

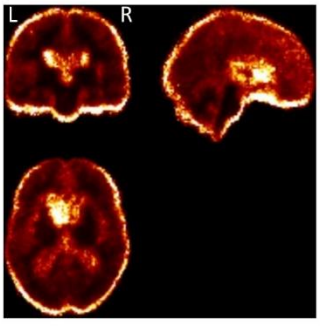
Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Exploring Dementia with Lewy Bodies through Deep Learning: Insights from structural MRI Data

Authors: B. AHMADI, Z. MORSHEDIZAD, M. REISI GAHROOEI, ***A. BABAJANI-FEREMI**;
Univ. of Florida, Gainesville, FL

Abstract: The intricate nature of dementia with Lewy bodies (DLB) presents diagnostic and management challenges. Despite being the second most common form of neurodegenerative dementia, significant gaps persist in understanding its pathophysiology and differentiating it from other dementia subtypes. To address this gap, our study explores the potential of deep learning (DL) via structural MRI (sMRI) to delineate DLB's hallmark features—cognitive fluctuations (CF), visual hallucinations (VH), and REM sleep behavior disorder (RSBD)—and to distinguish DLB from Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal cognition (CN). Analyzing sMRI data from a cohort of n = 5,454 subjects sourced from the National Alzheimer's Coordinating Center databases (**Fig. 1**), we employed a 3D Convolutional Neural Network to predict brain age across these groups using skull-striped MRIs as input. The model's architecture featured convolutional layers with ReLU, max-pooling, and batch normalization, ending with global pooling and dense layers. Initially trained and validated on CN data, the model was later applied to predict brain age in MCI, DLB, and AD patients, as well as in a CN test set. Results revealed a wider age gap (AG)—the difference between chronological age and the predicted brain age—in DLB, AD, and MCI compared to CN ($P < 10^{-9}$; **Fig. 1**). Moreover, DLB and AD demonstrated wider AGs than MCI ($P < 10^{-5}$), with DLB also wider than AD ($P < 0.012$). In the DLB cohort, patients with VH exhibited a larger AG than those without (4.21 yr; $P < 0.027$). Similarly, patients with CF and RSBD showed a trend towards a larger age gap (2.59 yr and 1.86 yr, respectively) compared to those without, though statistical significance was not achieved ($P > 0.2$). Additionally, saliency maps highlighted brain regions associated with CF, VH, and RSBD (see **Fig. 1** for a saliency map related to VH). These findings underscore the potential of DL in early characterization of diverse dementia pathologies and in elucidating DLB-specific symptoms, offering valuable insights for improved patient care and management.

	CN	MCI	AD	DLB
n	2899	547	1931	77
Sex [Male, Female]	977, 1922	221, 326	876, 1055	61, 16
Age [Mean ± STD] (year)	69.24 ± 10.69	72.69 ± 9.68	74.32 ± 9.12	74.74 ± 7.73
Absolute age gap [Mean ± STD] (year)	5.91 ± 5.18	7.47 ± 5.42	8.75 ± 6.65	10.33 ± 6.59
Age gap [Mean ± STD] (year)	0.71 ± 7.82	4.32 ± 8.16	6.7 ± 8.71	9.16 ± 8.14



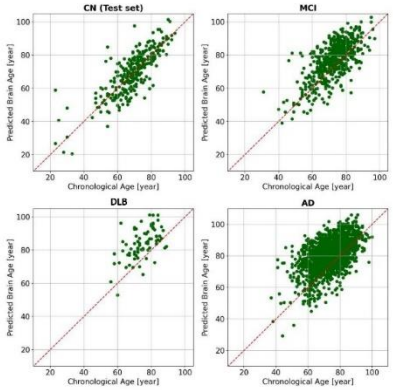


Fig. 1. Analysis overview and results visualization. (Top) Summary table presenting demographic information and the age gap of subjects analyzed. (Bottom-Right) Four subplots illustrating the predicted brain age versus chronological age for healthy controls (HC) and patients with mild cognitive impairment (MCI), dementia with Lewy bodies (DLB), and Alzheimer's disease (AD). (Bottom-Left) Saliency map highlighting MRI features associated with visual hallucinations in DLB patient.

Disclosures: B. Ahmadi: None. **Z. Morshedizad:** None. **M. Reisi Gahrooei:** None. **A. Babajani-Feremi:** None.

Poster

PSTR448: Alzheimer's Disease: Clinical and Pre-Clinical Imaging Studies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR448.18/C92

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

Support: NIH k23 AG070320-07A1

Title: Microstructural but not macrostructural damage is associated with antisocial behavior in bvFTD patients

Authors: *B. AKBARIAN, K. HETT, J. LEE, T. PHAN, R. DARBY;
Vanderbilt Univ., Nashville, TN

Abstract: Antisocial behaviors are common symptoms in behavioral variant frontotemporal dementia patients (bvFTD) and may occur early in the disease, prior to obvious brain atrophy on MRI. Here, we hypothesize that grey matter microstructural changes may occur prior to macrostructural brain atrophy in the early stages of bvFTD and will relate to the severity of antisocial behaviors. T1-weighted images were used to extract microstructural information through texture analysis in 32 bvFTD, 23 AD patients and 76 healthy controls. Antisocial behavior was measured using the social behavior questionnaire (SBQ). We restricted analysis to orbitofrontal cortex (OFC) and ventromedial prefrontal *a priori* brain regions known to be structurally abnormal in bvFTD patients and associated with antisocial behaviors in other patient groups. Linear regressions were used to find the relationship between volumetric and texture measures and SBQ scores, adjusted for age and gender (and ICV for volumetric analysis). Then, patients were categorized into high and low antisocial behavior groups. An ANCOVA was performed to compare texture feature between healthy controls and patients with low and high levels of antisocial behavior. There were no significant relationships between frontal brain volumes and antisocial behavior (Fig. 1A), nor were there brain volumetric differences between patients and healthy controls in our sample (Fig. 1C). In contrast, we found a positive correlation between texture features and antisocial behavior in the left lateral OFC (Fig 1B), with patients with both low and high levels of antisocial behavior showing reduced autocorrelation compared to cognitively healthy subjects (Fig. 1D). Our findings suggest that microstructural alterations may precede macrostructural changes in bvFTD and that problematic antisocial behaviors may occur specifically with early microstructural changes, highlighting the potential of using texture analysis as a biomarker for early diagnosis of dementia.

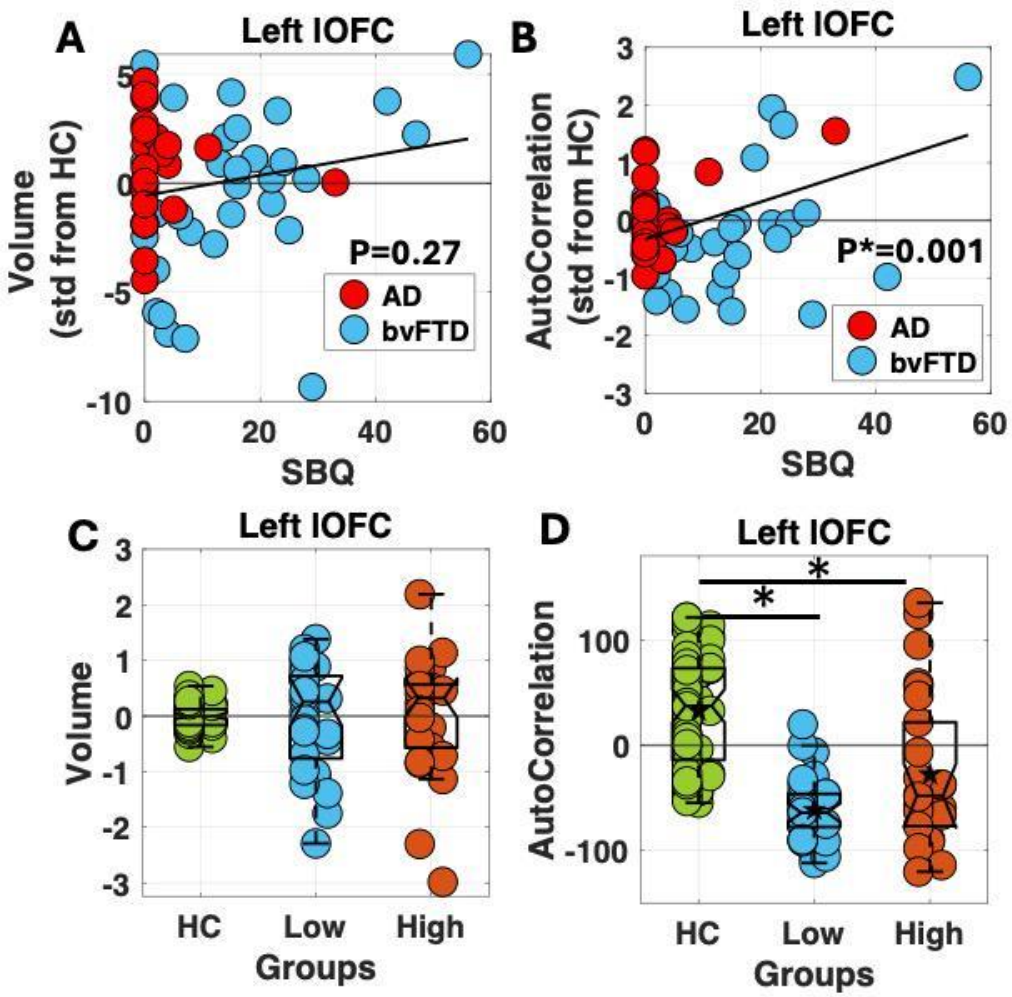


Figure 1: **A**: The relationship between Social Behavior Questionnaire (SBQ) scores and volume ($p<0.05$, corrected, $\alpha = 0.05/6 = 0.0083$). **B:** The relationship between SBQ scores and autocorrelation ($p>0.05$). **C**: The comparison of volume between healthy control (HC), and patients with low and high SBQ scores. *: $p<0.05$, uncorrected. **D**: The comparison of autocorrelation between healthy control (HC), and patients with low and high SBQ scores. lOFC: lateral orbitofrontal cortex.

Disclosures: B. Akbarian: None. **K. Hett:** None. **J. Lee:** None. **T. Phan:** None. **R. Darby:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.01/C93

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

Support: National Research Foundation (NRF) (RS-2023-00223559)
Korea Health Industry Development Institute (KHIDI) (RS-2023-00267453)

Title: Effect of a salicylic acid derivative, KBN-2202, on changes of Alzheimer`s disease-related factors in murine neuroblastoma Neuro2a cells

Authors: *J. KIM[1,2,3], J.-H. HEO[1,2,3], M. KIM[2,3], M. CHOI[3,4], S.-R. LEE[1,2,3,4];
[1]Dept. of Biomed. Sci., [2]Dept. of Pharmacol., [3]Efficacy Test Ctr. for Mental & Behavioral Disorders (MBD), [4]Lab. Animal Res. Ctr., Ajou University, Sch. of Med., Suwon, Korea, Republic of

Abstract: Effects of a salicylic acid derivative, KBN-2202, on changes of Alzheimer's disease-related factorsin murine neuroblastoma Neuro2a cells Ji Hun Kim[1,2,3], Jeong-Hyeon Heo[1,2,3], Moonhang Kim[2,3], Mi Ran Choi[3,4*], Sang-Rae Lee[1,2,3,4*1]Department of Biomedical Science, Ajou University School of Medicine, Suwon, Republic of Korea[2]Department of Pharmacology, Ajou University School of Medicine, Suwon, Republic of Korea[3]Efficacy Test Center for Mental & Behavioral Disorders (MBD), Ajou University School of Medicine, Suwon,Republic of Korea[4]Laboratory Animal Research Center, Ajou University School of Medicine, Suwon, Republic of Korea*Correspondence: lsr21@ajou.ac.kr; mrchoi2007@ajou.ac.krAlzheimer's disease (AD) is a neurodegenerative disease that has a serious impact on daily life, showing various symptoms such as memory loss, language impairment, and decreased judgment. Recently, AD treatments have focused on alleviating symptoms through neurotransmitter regulation. However, considering that AD is caused by multi-factorial mechanisms, multi-target strategies must be proposed to develop new drugs for AD. In this study,we aimed to investigate whether the novel salicylic acid derivative, KBN-2202, exhibits multi-targeting effects on Neuro2a cells. After exposing Neuro2a cells to KBN-2202 for 24 h, cell viability, acetylcholine (ACh) production, acetylcholinesterase (AChE) activity, and expression levels of genes involved in AD pathology were analyzed. In addition, nitric oxide (NO) production was measured in murine microglial BV2 cells. The concentration of ACh was significantly increased but the activity of AChE was significantly inhibited in Neuro2a cells exposed to KBN-2202. Furthermore, KBN-2202 not only alleviated the production of NO induced by LPS but also led to down-regulation of genes such as *App*, *Tau*, *Psen1*, and *Psen2*. In conclusion, KBN-2202 exhibits multi-targeting effects on multi-factorial mechanisms involved in AD pathology, suggesting its potential as a new therapeutic drug for AD.

Disclosures: J. Kim: None. **J. Heo:** None. **M. Kim:** None. **M. Choi:** None. **S. Lee:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.02/C94

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

Support: National Research Foundation (NRF) (RS-2023-00223559)
Korea Health Industry Development Institute (KHIDI) (RS-2023-00267453)

Title: Effects of KBN-2201 on pathological mechanisms of Alzheimer's disease in murine neuroblastoma Neuro2a cells

Authors: *J.-H. HEO[1,2,3], J. KIM[4,3], M. KIM[4,3], M. CHOI[5,6], S.-R. LEE[4,3,6];
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Abstract: Effects of KBN-2201 on Pathological Mechanisms of Alzheimer’s Disease in MurineNeuroblastoma Neuro2a Cells Jeong-Hyeon Heo[1,2,3], Ji Hun Kim[1,2,3], Moonhang Kim[2,3], Mi Ran Choi[3,4*], Sang-Rae Lee[2,3,4*1]Ajou University, Suwon-si, Republic of Korea[2]Department of Pharmacology, Ajou University School of Medicine, Suwon, Republic of Korea[3]Efficacy Test Center for Mental & Behavioral Disorders (MBD), Ajou University School of Medicine, Suwon,Republic of Korea[4]Laboratory Animal Research Center, Ajou University School of Medicine, Suwon, Republic of Korea*Correspondence: lsr21@ajou.ac.kr; mrchoi2007@ajou.ac.krAlzheimer's disease (AD) is a neurodegenerative disorder that heavily impacts daily life, characterized bysymptoms like memory loss, impaired judgment, and language difficulties. Although recent treatments for ADhave predominantly focused on mitigating symptoms by regulating neurotransmitters, the intricate complexity ofAD necessitates the exploration of multi-target approaches in drug development. This study aimed to investigatewhether the novel derivative of 2-hydroxy-4-(trifluoromethyl) benzoic acid, KBN-2201, exhibits multi-targetingeffects on Neuro2a cells. Following a 24-hour exposure to KBN-2201, we assessed cell viability, acetylcholine(ACh) production, acetylcholinesterase (AChE) activity, and the expression of genes associated with ADpathology in Neuro2a cells. Besides, we measured nitric oxide (NO) production in murine microglial BV2 cells.Our results revealed a significant increase in ACh concentration and notable inhibition of AChE activity inNeuro2a cells treated with KBN-2201. Moreover, KBN-2201 not only mitigated the production of NO inducedby LPS but also led to the down-regulation of key genes such as *App*, *Tau*, *Psen1*, and *Psen2*. In conclusion, KBN-2201 demonstrates promising multi-target effects on the complex mechanisms involved in AD pathology,suggesting its potential as a novel therapeutic agent for AD.**Keyword**Alzheimer's disease, acetylcholine, KBN-2201, multi-targeting effects

Disclosures: J. Heo: None. **J. Kim:** None. **M. Kim:** None. **M. Choi:** None. **S. Lee:** None.

Poster

PSTR449: Alzheimer’s Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.03/C95

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

Support: AMED grant 24gm6410017 and 24dk0207073
JSPS grant 23K21357

Title: Evaluation of the pharmacological effects of photo-oxygenation on intracellular aggregated tau

Authors: *M. KURIYAMA[1], T. SAWAZAKI[2,3], Y. SOHMA[2,3], M. KANAI[2], Y. HORI[1], T. TOMITA[1];
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Abstract: Tauopathies are a group of neurodegenerative diseases in which tau protein abnormally aggregates, becomes insoluble, and accumulates intracellularly. Because this aggregation and accumulation of tau leads to neuronal cell death and contributes to disease pathogenesis, methods to reduce aggregated tau are useful as a therapeutic strategy. As such method, we have developed an original method called the "photo-oxygenation method" in which we use a light-activatable small compound. We have shown that aggregated tau oxygenated by a photo-oxygenation catalyst Cat O was cleared more rapidly in the PS19 tauopathy mouse model. These results suggest the utility of photo-oxygenation as a treatment for tauopathy. However, the dose-response relationship of photo-oxygenation remains unknown. In this study, we analyzed the catalyst concentration and light doses required for the pharmacological effect of photo-oxygenation in a cultured cell system. We used a murine neuroblastoma Neuro2a cell line that stably expressing a Venus added to the C-terminus of full-length human tau with the P301S mutation, an aggregation-promoting mutation, as a cultured cell system in which we evaluated the clearance of aggregated tau. We induced intracellular tau aggregates by transfection of the tau seeds prepared from pre-aggregating recombinant tau. The aggregation of tau was confirmed by the appearance of highly positive Venus bright spots in immunocytochemical analysis and sarkosyl-insoluble phosphorylated tau in biochemical analysis. After 24 hours of tau aggregation, we performed the photo-oxygenation reaction on living cells by administration of Cat O and light irradiation. The intracellular tau aggregates were removed in a catalyst concentration- and light irradiation-dependent manner. We identified that the EC50 of Cat O was 400 nM, and ED50 of light was 31.92 J/cm^2, respectively. Together, these results allowed us to estimate the appropriate photo-oxygenation reaction conditions for the treatment of tauopathy.

Disclosures: M. Kuriyama: None. **T. Sawazaki:** None. **Y. Sohma:** None. **M. Kanai:** None. **Y. Hori:** None. **T. Tomita:** None.

Poster

PSTR449: Alzheimer’s Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.04/C96

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

Support: NSF GRFP, Grant No. 1937963
VMAC Pilot and Feasibility Funding Program, Award No. P20-AG068082
SyBBURE Searle Undergraduate Research and Design Program

Title: Synthetic receptors for programmable tau-responsive cellular therapies

Authors: *D. J. CONGER, M. R. SPETZ, J. M. BRUNGER;
Dept. of Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: Tauopathies account for the vast majority of dementia cases worldwide. Current therapies do not affect underlying disease mechanisms. Despite their ability to bind and clear tau, anti-tau monoclonal antibodies (mAbs) have shown lackluster results in clinical trials. This research seeks to unite the specificity anti-tau mAbs with the power of gene therapies by engineering cells capable of detecting extracellular tau and responding with the expression of customizable transgenes. Cells were programmed using receptors constructed from intramembrane proteolysis receptor platforms, such as synNotch or SNIPR. Both platforms enable the customization of cell behaviors by replacing the extracellular domain and intracellular domain of the Notch mechanoreceptor with bespoke recognition domains and synthetic transcription factors, respectively. Receptors with recognition domains derived from clinical anti-tau mAbs (semorinemab, gosuranemab, bepranemab) were built and expressed in mouse mesenchymal stromal cells (mMSCs) (**Fig 1A**; synNotch constructs displayed). Engineered cells were plated on passively adsorbed full-length recombinant human tau (rhTau), and receptor activation by rhTau resulted in expression of either a SEAP+mCherry or a BDNF+mCherry transgene cassette. All synNotch receptors recognized rhTau, as indicated by SEAP and mCherry expression (**Fig 1B**). After replacing the SEAP transgene with a brain-derived neurotrophic factor (BDNF) transgene, rhTau instead stimulated expression of BDNF (**Fig 1C**). Receptors with a shorter transmembrane domain (Sem-SNIPR; **Fig 1D**) or with an alternate intracellular domain (Sem-Notch-Gal4; **Fig 1D**) enact comparable expression of SEAP and mCherry. Our results demonstrate that tau-sensitive receptors enable programming of cellular responses to extracellular tau. We envision tau receptors being used in a cell-based therapy, outfitting microglia and astrocytes with novel therapeutic behaviors. In neurons, tau receptors may serve as useful tools for reporting the extent of local tau pathology in real-time.

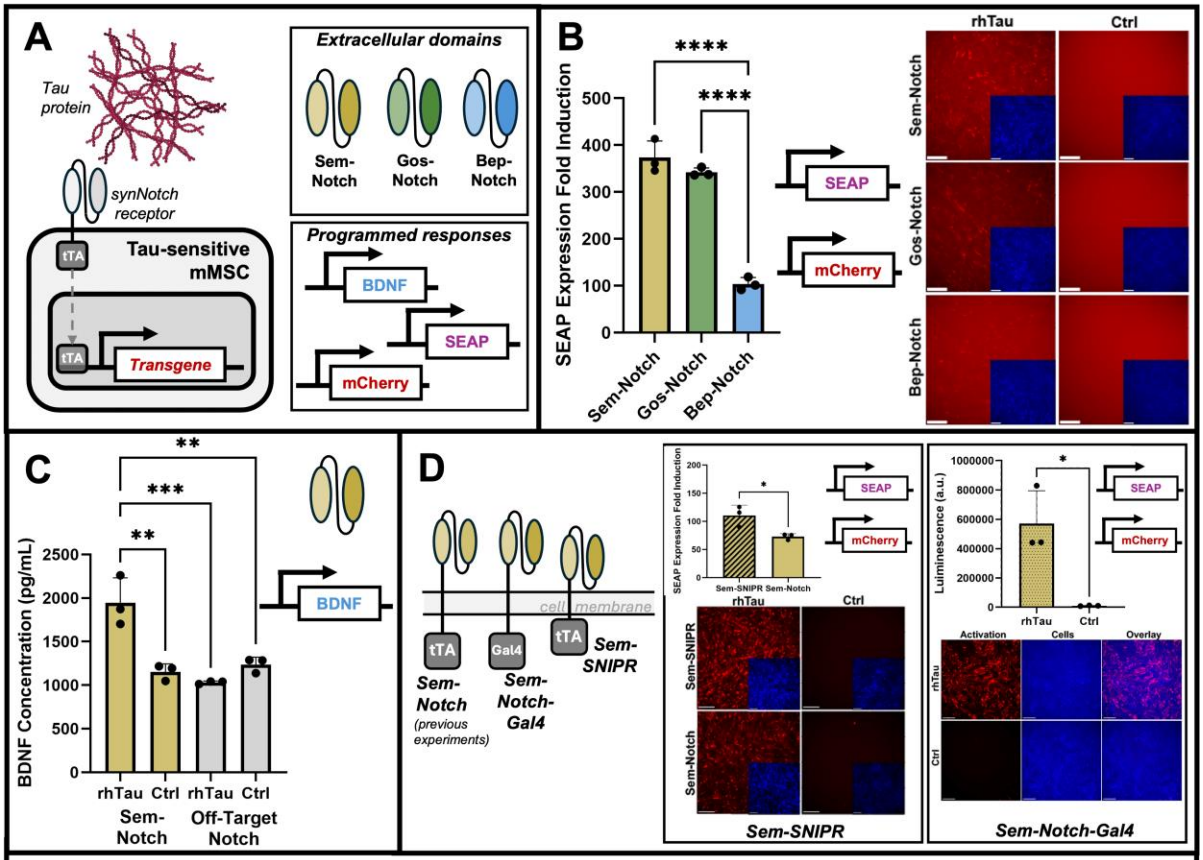

Figure 1. Anti-tau intramembrane proteolysis receptors program tau-sensitive transgene expression in mMSCs. A: SynNotch receptors were constructed from tau-specific recognition domains before being wired to SEAP, mCherry, or BDNF transgenes in mMSCs. **B:** mMSCs expressing anti-tau synNotch receptors demonstrate substantial reporter upregulation in response to plate-immobilized rhTau. Tukey's test; ****p < 0.00005. Scale bar = 200 µm. **C:** Cells expressing a Sem-Notch receptor enacted expression and secretion of BDNF in response to immobilized rhTau. No response to tau was detected in similar cells expressing an off-target synNotch receptor. Tukey's test; **p < 0.005, ***p < 0.0005. **D:** In Figure 1A-C, cell behaviors were directed by a synNotch receptor with a tTA intracellular domain. Alternate constructs, such as a Sem-SNIPR or a Sem-Notch receptor with a Gal4 intracellular domain, also enact cellular responses to immobilized rhTau. Sem-SNIPRs enact higher fold induction than Sem-Notch receptors in response to rhTau treatment. Unpaired t-test; *p < 0.05. Scale bar = 200 µm.

Disclosures: D.J. Conger: None. **M.R. Spetz:** None. **J.M. Brunger:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.05/C97

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

Support: NIH Grant R03AG075597
DOD Grant HT9425-23-1-0043

Title: Development of a novel gene therapy for the treatment of tauopathies in a cellular system

Authors: *H. SINGH[1,2], J. XIAO[3], A. DAS[4], T. POURMOTABBED[3], M. KHAN[3];
[1]Biotech. & Neurol., Delhi Technological Univ. & Univ. of Tennessee Hlth. Sci. Ctr., Delhi, India; [2]Neurology, University of Tennessee Health Science Center, Memphis, TN; [3]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [4]Delhi Technological Univ., Delhi, India

Abstract: Development of a novel gene therapy for the treatment of tauopathies in a cellular system

Himanshi Singh, Jianfeng Xiao, Asmita Das, Tayebeh Pourmotabbed*, Mohammad Moshahid Khan*

Background: Tauopathies, including Alzheimer disease (AD) and Frontotemporal Dementia (FTD), are a group of neurological disorders characterized by accumulation of aberrant tau protein and cognitive deficits. The development of tauopathies cannot currently be stopped or slowed down by treatment measures. Thus, there is a critical need to identify potential disease-modifying treatments that provide a higher quality of life for individuals affected with tauopathies. Given the importance of tau protein in tauopathies, tau-based therapy that regulates overwhelming pathological tau protein production is a potentially impactful approach to counter tauopathies. DNAzyme (DNZ), a catalytically active RNA-cleaving single-stranded DNA oligonucleotide is emerging as a potential gene-silencing approach for various therapeutic purposes, and we have been developing DNZ technology to lower production and aggregation of pathological tau protein, the causal agent in tauopathies.**Methods:** We designed and constructed anti-Tau DNAzymes (TDNZ) against human microtubule-associated protein tau (*MAPT*) gene and established their efficacy in cleaving human tau mRNA by i*n vitro* testing. We further determine the impact of TDNZ on expression levels of tau mRNA and protein as well as safety profile of TDNZ in SH-SY5Y cells. RT-qPCR, MTS cytotoxicity assay and ELISA methods were used to examine the effect of TDNZ on tau level and cytotoxicity.**Results:** TDNZ cleaved Tau transcripts expressed from human tau cDNA in pCMV3 with high efficiency (>95%) in vitro, reduced mRNA and protein levels of human tau in SH-SY5Y cells. The preclinical cytotoxicity studies showed that the TDNZ is safe, no significant toxicity in cellular system was observed. **Conclusion:** These data suggest that DNAzyme based therapy holds the potential for the treatment of tauopathies. The safety and therapeutic benefit of DNAzyme in preclinical models of tauopathies are in process.**Funding:** This work was supported by National Institute of Health grant number R03AG075597 and Department of Defense Award Number HT9425-23-1-0043.

Disclosures: H. Singh: None. **J. Xiao:** None. **A. Das:** None. **T. Pourmotabbed:** 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 grant number R03AG075597, Department of Defense Award Number HT9425-23-1-0043. **M. Khan:** 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 grant number R03AG075597, Department of Defense Award Number HT9425-23-1-0043.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.06/C98

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

Support: Cinvestav-UC Call for Collaborative Research Proposals

Title: A bifunctional peptide against Alzheimer´s disease: interactions with copper-binding proteins

Authors: V. LOPEZ GUERRERO, Sr.[1], Y. POSADAS[2], C. SÁNCHEZ-LÓPEZ[3], A. SMART[4], K. SINGEWALD[4], C. DEN AUWER[5], G. MILLHAUSER[6], L. QUINTANAR[2], *J. SEGOVIA-VILA[7];
[1]Physiology, Biophysics and Neurosci., Ctr. for Res. and Advanced Studies (Cinvestav), Mexico City, Mexico; [2]Cinvestav, Mexico city, Mexico; [3]Cinvestav, Mexico, Mexico; [4]UCSC, Santa Cruz, CA; [5]Univ. Cote d´ Azur, Nice, France; [6]Univ. of California, Santa Cruz, Santa Cruz, CA; [7]Cinvestav-IPN, Mexico 07300 DF, Mexico

Abstract: Alzheimer's disease (AD) is the most frequent neurodegenerative disease and the seventh cause of death worldwide. One of the main features of AD is the accumulation of the amyloid beta (Aβ) peptide, produced by the proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases. Interestingly, APP, β-secretase (BACE1), and Aβ peptide are copper-binding proteins: APP binds three Cu^{2+} ions at its extracellular domain, β-secretase likely transports Cu^{1+} ions through its transmembrane domain, and Aβ binds one Cu^{2+} ion at its N-terminal region. Consistently, copper homeostasis in AD patients is altered: copper is increased in Aβ plaques, it is scarce in regions with neurodegeneration, and labile copper is increased in blood. In this context, removing or preventing copper accumulation in Aβ plaques has been proposed as a therapeutic strategy to restore copper homeostasis in AD. However, in the last decade, another Cu^{2+}-binding protein, the Cellular Prion Protein (PrP^{C}) has been implicated in AD: PrP^{C} down-regulates N-methyl-D-aspartate (NMDA) receptors through a Cu^{2+}-dependent mechanism, that is disrupted by Aβ. Therefore, designing molecules that target the Cu^{2+}-Aβ interaction without altering the function of Cu^{2+}-binding proteins—such as PrP^{C}—is a challenge. In this study, we present an innovative approach using a combination of spectroscopic tools and cell culture studies to characterize and optimize a tetrapeptide (TP) that removes Cu^{2+} from Aβ and modulates Cu^{2+}-induced aggregation.

Disclosures: V. Lopez guerrero: None. **Y. Posadas:** None. **C. Sánchez-López:** None. **A. Smart:** None. **K. Singewald:** None. **C. Den auwer:** None. **G. Millhauser:** None. **L. Quintanar:** None. **J. Segovia-Vila:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.07/C99

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

Title: Accelerated Aging and senescence in cerebral organoids

Authors: *T. LÖFFLER[1], I. ITXASO[1], M. DAURER[1], S. FLUNKERT[2], M. PROKESCH[1]; [2]Neuropharm., [1]Scantox Neuro GmbH, Grambach, Austria

Abstract: Age-related accumulation of senescent cells in the nervous system is relevant for the onset and progression of neurodegenerative diseases and has recently even been addressed in clinical Alzheimer’s disease trials. Since most neurodegenerative diseases are age-associated, the use of translatable models that reflect aspects of senescence and aging are of high relevance in the field. Brain organoids, self-organized three-dimensional aggregates derived from human induced pluripotent stem cells (iPSC), have emerged as a novel and translational model for studying human brain development and developmental diseases. Utilizing this complex tool to also model neurodegenerative diseases is an emerging field and has opened new dimensions for understanding genetic disease components. However, the use of organoids as a model system in this field also contains certain challenges and limitations, as cells are juvenile and may not be fully mature for a certain time span. To overcome this issue, we used D-galactose treatment to accelerate aging and induced senescence in human brain organoids. Immediate effects such as a reduced proliferation of stem cells and as a result, a reduced size of organoids of up to 50% were observed, depending on the timepoint and duration of treatment. Additionally, senescence markers including β-galactose activity, assessed via a 4-MUG-based assay, as well as p53 and p21 levels were analysed and highlight increased senescence due to long-term D-galactose lesion. In addition, DNA damage, and changes in reactive oxygen species and mitochondrial activity in the presence or absence of senolytic drugs will be investigated in this model. Overall D-galactose treatment of cerebral organoids leads to increased senescence and changes in age-associated biomarkers as analysed by different methods. Accelerated aging of cerebral organoids can serve as a valuable tool in drug development by providing a faster and more efficient means of testing potential therapeutics for age-related neurological conditions such as Alzheimer's disease.

Disclosures: T. Löffler: A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **I. Itxaso:** A. Employment/Salary (full or part-time):; Scantox Neuro. **M. Daurer:** A. Employment/Salary (full or part-time):; Scantox Neuro. **S. Flunkert:** A. Employment/Salary (full or part-time):; Scantox Neuro. **M. Prokesch:** A. Employment/Salary (full or part-time):; Scantox Neuro.

Poster

PSTR449: Alzheimer’s Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.08/C100

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

Support: NIH Grant R01AG059854

Title: Drug screening in iPSC-derived neurons: Identifying therapeutic candidates for Alzheimer's disease using bioinformatic approaches

Authors: *H. M. BUCHANAN[1,2], E. YOUTH[2], T. LAM[1,2], A. ROPRI[1,2], A. BARTOSCH[1,2], C. KARAN[3], M. KAUFMAN[2], H. LI[3], A. SPROUL[1,2], A. F. TEICH[1,2,4];
[1]Pathology and Cell Biol., [2]Taub Inst. for Res. on Alzheimer's Dis., [3]Systems Biol., [4]Neurol., Columbia Univ., New York, NY

Abstract: Alzheimer's disease (AD) is characterized by the accumulation of beta-amyloid containing plaques and hyperphosphorylated tau-based tangles. Unfortunately, pharmacological attempts at addressing these pathological hallmarks have been largely unsuccessful, thus highlighting the need to target additional disease-reputed pathways, mechanisms and targets. In order to do so, we here utilized bioinformatic tools to generate a hiPSC-derived neuronal interactome from Ngn2-transdifferentiated neurons and subsequently conduct, within the same model platform, a high-throughput drug screen of ~1000 FDA and non-FDA approved drugs using PLATE-seq. Accordingly, our resulting database includes predicted regulons for every transcriptional regulator (MRs; n=5489) within our neuronal transcriptome and, importantly, over 1000 pharmacological data points for each. Through querying this dataset, we identified compounds which manipulate disease-associated MRs and may function as candidate targets for therapeutic development. Our hypothesis is that our identified compounds will rescue phenotypes associated with AD hiPSC neurons, namely increased phospho- tau levels, enhanced neurogenesis and altered early endosome size, which we believe are functionally interrelated. Indeed, western blot analysis revealed a significant reduction of Ser202, Thr231 and Ser396/404 phospho-tau levels in compound treated vs. control hiPSC groups. Additionally, immunofluorescence analysis found reduced expression of MAP2 positive staining in AD vs. control lines following drug treatment, suggestive of a "rescue" of accelerated neurogenesis. Moreover, initial examination of early endosomes found that compound treatment in AD lines returned endosome size to levels seen in isogenic control cells. Analysis to further validate the above findings is ongoing. Taken together, we employed an integrated approach to identify drug candidates for the treatment of AD and identified compounds that are capable of rescuing key AD-relevant phenotypes in hiPSC-derived neurons.

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Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.09/C101

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

Support: RO1 AG061708

Title: The promise of small molecule therapeutics for Alzheimer's: Innovative inhibitors targeting amyloid-β oligomers pathology

Authors: *R. NOWAR[1], E. JOHNSON[2], K. DU[3], W. L. KLEIN[3], R. SILVERMAN[2];
[1]Neurobio. and Chem., [2]Chem., [3]Neurobio., Northwestern Univ., Evanston, IL

Abstract: The complexity in the underlying pathophysiological mechanisms of Alzheimer's disease (AD) has introduced difficulty in disease prevention and treatment. Many therapeutic strategies have been explored for several decades in clinical trials, but disease-modifying drugs for Alzheimer's disease are limited. During the past decade, research efforts have focused on soluble Aβ oligomers (sAβO). The accumulating body of evidence suggests that sAβOs play a pivotal role in driving downstream pathology in AD, including the aberrant phosphorylation of tau (p-tau), neurodegeneration, disruption in synaptic signaling, cognitive decline, and inflammatory responses. The hypothesis of intracellular Aβ accumulation and insufficient lysosomal degradation has begun to gain significant attention in recent years, where it has been reported that this pathology can spread between cells through cell-to-cell contact via the release of extracellular vesicles (EVs). Targeting AβOs-mediated toxicity or spread occurring at early disease stages may represent a promising therapeutic strategy for AD. Development of small molecule therapeutics has been hampered by challenges such as compromised efficacy and identification of specific therapeutic targets. Here we present two novel small molecule inhibitors that have been shown to ameliorate Aβ toxicity and improve neuronal health via two different mechanisms. First, is HD-3-86, a potent nNOS inhibitor that blocks AβO-induced ptau accumulation and neuronal death in primary hippocampal neurons and HT22 cells at sub-micromolar concentrations. Second is NU-9, a drug candidate that has been approved for Phase 1 clinical trials for ALS, which we showed reduces neuronal binding of AβOs by 80% in cultured hippocampal neurons treated with Aβ monomer. Using multi-labelling immunofluorescence studies, highly specific AβO antibodies and immunoblotting experiments, both molecules have shown promising results for blocking Aβ-mediated downstream pathology. Our findings represent significant discoveries for the NU-9 mechanism of action regarding its multiple protein targets in ALS and AD. We further demonstrate the substantial potential neuroprotective and therapeutic benefit of targeting early pathological pathways mediated by Aβ oligomerization prior to plaque formation in AD.

Disclosures: R. Nowar: None. **E. Johnson:** None. **K. Du:** None. **W.L. Klein:** None. **R. Silverman:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.10/C102

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

Support: CIHR grant (MOP-84480)

Title: Amyloid β-induced toxicity and endo-lysosomal markers: Potential role of native PLGA nanoparticles

Authors: *S. KAR[1], R. MALLESH[2], X. LI[1];
[1]Med. (Neurology), Univ. of Alberta, Edmonton, AB, Canada; [2]Fac. of Med., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Evidence suggests that increased levels/aggregation of beta-amyloid (Aβ) peptides initiate degeneration of neurons and development of Alzheimer's disease (AD), the most common cause of dementia affecting the elderly population. At present, the cause of neuronal vulnerability in selected brain regions remains unclear. The endo-lysosomal system has long been suggested to play a critical role in the loss of neurons in AD brains. Accumulated data suggest that altered activity of the endo-lysosmal system can enhance the level/aggregation of Aβ peptide which can trigger lysosomal leakage leading to the loss of neurons *via* release/activation of lysosomal enzymes including cathepsins D (CatD) into the cytosol. Thus, many studies have pursued small molecules including nanoparticles conjugated with drugs/agents such as phytochemicals, hormones, metal chelators to prevent Aβ aggregation/toxicity, as a treatment strategy for AD. In contrast to drug-conjugated nanoparticles, we recently reported that native acidic poly (D,L-lactide-co-glycolide)(PLGA) nanoparticles, which constitute a family of FDA-approved biodegradable polymers, can attenuate Aβ aggregation/toxicity in cellular/animal models of AD. In this study, we evaluated if PLGA nanoparticles can protect cultured neurons against Aβ-mediated toxicity by influencing endosomal system. Our results show that native PLGA can alter the cellular levels of endosomal (Rab7), autophagic (LC3II) and lysosomal (LAMP1, TFEB) markers in Aβ-treated mouse cortical cultured neurons. Addiaionally, PLGA treatment can attenuate enhanced cytosolic levels of CatD in Aβ-treated neurons. Collectively, these results suggest that native PLGA nanoparticles by regulating endo-lysosomal system can influence neuronal viability against Aβ toxicity, thus highlighting their potential use in the treatment of AD pathology

Disclosures: S. Kar: None. **R. Mallesh:** None. **X. Li:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.11/C103

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

Support: NIH Grant AG079838
NIH Grant AG015379

Title: A novel time-lapse live cell imaging assay for reporting neuronal vulnerability

Authors: *M. YOKOMIZO, N. WIECKIEWICZ, M. SADEK, S. TORRES, O. BEREZOVSKA, M. MAESAKO;
MassGeneral Inst. for Neurodegenerative Dis., Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Some neurons die, while some survive in neurodegenerative diseases such as Alzheimer's disease (AD). However, the underlying molecular mechanism behind neuronal vulnerability and resilience is unclear. This could be, in part, because there are a few assays available for the quantitative detection of vulnerable neurons. Here, we report the development and validation of a straightforward, time-lapse live cell imaging assay utilizing propidium iodide (PI) under oxidative stress, which allows the "visualization" and "quantification" of neuronal death (i.e., disruption of the membrane integrity) on a cell-by-cell basis. Using this novel assay, we show that each neuron displays a distinct susceptibility to oxidative stress. Furthermore, we found that endo-lysosomes could be one of the upstream regulators of neuronal vulnerability. Our assay would provide exciting opportunities to explore the molecular basis underlying neuronal vulnerability and resilience, and develop novel therapeutic strategies for neurodegenerative diseases.

Disclosures: M. Yokomizo: None. **N. Wieckiewicz:** None. **M. Sadek:** None. **S. Torres:** None. **O. Berezovska:** None. **M. Maesako:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.12/C104

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

Support: PRIN 2022 PNRR, Prot. P202278YHJ

Title: Understanding the Influence of a Naturally Occurring Dominant-Negative Variant of DNA Polymerase-β on Alzheimer's Disease

Authors: R. SANTANGELO[1], M. GRASSO[2], S. MERLO[1], A. FIDILIO[1], L. DE PLANO[3], A. CACCAMO[3], F. CARACI[1], S. ODDO[3], ***A. COPANI**[1];
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Abstract: Evidence from various system models converges to suggest a direct association between neurodegeneration in Alzheimer's disease (AD) and disruptions in cell cycle regulation with aberrant DNA replication (Herrup et al., J. Neurosci. 24, 2004). Specifically, research indicates that amyloid-beta (Aβ)-mediated neuronal apoptosis relies on the activation of the cell cycle and neuronal DNA replication. We have previously shown that the DNA repair enzyme, DNA polymerase-β (DNA pol-β), is implicated in facilitating DNA replication in Aβ-treated

neurons and contributes to the abnormal activation of DNA replication in neurons undergoing degeneration (Copani, et al., J. Neurosci. 26, 2006). A single gene on chromosome 8 encodes for DNA pol-β. Alternative splicing of the gene generates different isoforms, including Ex11Δ, which acts as a dominant negative regulator of DNA pol-β activity (Bhattacharyya and Banerjee, Proc. Natl. Acad. Sci. USA 94, 1997). DNA pol-β carries out the base-excision repair essential for DNA maintenance, so that deleting one copy of the gene, with ensuing reduced transcription of both the primary DNA pol-β and the Ex11Δ transcript, appears to increase susceptibility to AD-like pathology in mouse models (Sykora et al., Nucleic Acids Res. 43, 2015), We hypothesized that Ex11Δ DNA pol-β protects against AD by acting as a natural dominant-negative variant over the full-length DNA pol-β. We measured the transcripts of DNA pol-β and Ex11Δ DNA pol-β in peripheral blood lymphocytes from 40 AD patients (age range 56-90 years) and age-matched controls. Interestingly, RT-PCR analysis showed that the presence of the Ex11Δ DNA pol-ß increased with age in cognitively normal individuals but not in AD patients. Two different adeno-associated viruses expressing Ex11Δ DNA pol-ß have been generated to investigate whether the Ex11Δ DNA pol-ß reduces/abrogates the BER function of full-length DNA pol-ß in 92TAg mouse embryonic fibroblasts, and whether increasing Ex11Δ DNA pol-ß levels reduces/abrogates DNA replication carried out by full-length DNA pol-ß in cultured cortical neurons exposed to synthetic Aβ oligomers.

Disclosures: R. Santangelo: None. **M. Grasso:** None. **S. Merlo:** None. **A. Fidilio:** None. **L. De Plano:** None. **A. Caccamo:** None. **F. Caraci:** None. **S. Oddo:** None. **A. Copani:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.13/C105

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

Support: RF1 AG073418
R35 AG071734
R01 AG056259

Title: Effects of Small Molecule Autophagy Activators in hiPSC-Derived Cerebrocortical Organoids with AD-Associated APP Swedish and Presenilin 1 Mutations vs. Isogenic Control

Authors: *A. PRABHAVALKAR[1], S. LABRA[1], A. BALISTRERI[1], M. ALMARAZ[1], J. COMPHER[1], W. LIN[4], N. SCHORK[5], S. A. LIPTON[2], J. W. KELLY[3];
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Abstract: Alzheimer's disease (AD) affects the cognitive function of millions worldwide. The disease is notably characterized by an accumulation of abnormal protein aggregates. Current neurodegenerative therapeutics focus on targeting misfolded proteins in an effort to treat disease

pathology and restore cognitive function. These therapies, however, are often limited to a singular aspect of AD and lack a holistic approach to address disease pathology at multiple levels. Additionally, most disease models insufficiently recapitulate pathophysiological features of the human brain. In this study, we aimed to leverage autophagy, a highly-conserved cellular mechanism that enables abnormal protein degradation. In doing so, we were able to address some of the hallmark phenotypes characterized by AD in human induced pluripotent stem cell-derived cerebrocortical organoids (hiPSC-CO). We tested small molecule autophagy activators, including Rapamycin, Torin 1, and novel compounds, to ameliorate hyperphosphorylated tau levels in hiPSC-CO harboring familial AD mutations (APP^{SWE} or $PSEN1^{M146V}$). To quantify the effects of the autophagy activators, we evaluated the relative changes in autophagic flux and in downstream AD phenotype levels using protein quantification and fluorescent imaging-based techniques. The changes in autophagy activity and AD-related tauopathy were assessed in isogenic WT control and mutant hiPSC-CO genotypes. By tracking fluorescent dyes that incorporate into the membranes of autophagosomes and autolysosomes, we demonstrated increased rates of autophagy in hiPSC-CO treated with autophagy activators compared to corresponding control hiPSC-CO. Measuring the relative amounts of pathogenic protein, we found that autophagy-activating treatments decreased the level of hyperphosphorylated tau in mutant organoids. Our findings demonstrate that autophagy-promoting treatments may result in the mitigation of AD pathology in our hiPSC-CO disease model.

Disclosures: A. Prabhavalkar: None. **S. Labra:** None. **A. Balistreri:** None. **M. Almaraz:** None. **J. Compher:** None. **W. Lin:** None. **N. Schork:** None. **S.A. Lipton:** None. **J.W. Kelly:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.14/C106

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

Title: Fibroblast senescence in Alzheimer's Disease

Authors: *S. BEH, M. GULMEN, G. E. SERRANO, T. G. BEACH;
Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: Aging is considered the primary risk factor for several neurodegenerative diseases, including Alzheimer's disease (AD). Cellular senescence, a process where cells cease dividing and enter a state of permanent growth arrest due to stress or damage, plays an important role in the aging process and in age-related disorders like AD. The presence of senescent astrocytes, microglia, endothelial cells, and neurons has been observed in the brains of individuals with AD, as well as in AD animal models. Several studies indicate that AD is a systemic disorder that involves active communication between the brain and periphery, wherein pathways altered in brain cells also affect plasma, cerebrospinal fluid, and other peripheral cells of AD patients.

However, it remains unclear whether peripheral cells reproduce the cellular and molecular changes observed in the brain. In this study, we compared primary human dermal fibroblasts from individuals diagnosed with AD and healthy age-matched controls. Fibroblasts from both groups were cultured up to passage 15 to evaluate their cellular senescence characteristics. These fibroblasts were then examined for their growth, cell morphology, and various cellular functions, such as inflammation and apoptosis pathways, mitochondrial functions, and redox status. The senescence phenotype in aged AD fibroblasts was confirmed by elevated levels of β-galactosidase enzyme activity and an increase in senescence-related markers and cell cycle arrest indicators compared to control cells. Senescent AD fibroblasts exhibited decreased growth rates, longer population doubling times, faster growth plateau, and alterations in cell morphology, including increased cell size compared to control cells. Deficits in extracellular matrix production, increased proinflammatory and apoptosis markers, impaired mitochondrial structure and function, and accumulation of elevated levels of reactive oxygen species were observed in senescent AD fibroblasts. These results indicate that senescent fibroblasts could be used as an in vitro functional system, serving as a patient-derived peripheral model to replicate various cellular, molecular, and metabolic mechanisms involved in AD. This model could potentially serve as a translational tool for developing personalized medicine for AD.

Disclosures: S. Beh: None. **M. Gulmen:** None. **G.E. Serrano:** None. **T.G. Beach:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.15/C107

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

Support: Czech Science Foundation No. 22-24384S
Exregmed, project registration number CZ.02.01.01/00/22_008/0004562 (MEYS CR)

Title: Development and evaluation of N-methylpropargylamino-quinazoline compounds for Alzheimer's disease therapy

Authors: *M. HORAK[1], J. KORABECNY[2], O. SOUKUP[3];
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Abstract: Alzheimer's disease (AD) is a multifaceted disorder with an uncertain etiology. Current treatments, limited to cholinesterase inhibitors and N-methyl-D-aspartate receptor (NMDAR) antagonists, only alleviate symptoms. Due to the limited efficacy of therapies targeting a single molecule, a more effective strategy may be integrating multiple targets into a single compound, enhancing symptom management and potentially slowing disease progression.

This research involved the creation, synthesis, and biological analysis of 24 novel N-methylpropargylamino-quinazoline derivatives. In silico methods were initially utilized to evaluate these compounds for their oral bioavailability and potential effectiveness in the central nervous system. The *in vitro* tests assessed the impacts on cholinesterases, monoamine oxidase A/B (MAO-A/B), NMDAR antagonism, dehydrogenase activities, and glutathione levels. Furthermore, certain derivatives were tested for cytotoxic effects on undifferentiated and differentiated SH-SY5Y neuroblastoma cells. Compound II-6h was the most promising, with specific MAO-B inhibition, effective NMDAR antagonism, suitable cytotoxic levels, and the ability to cross the blood-brain barrier (BBB). Applying a structure-guided drug design approach in this study offers a new perspective on rational drug discovery, significantly enriching our strategies for developing advanced therapeutic solutions for AD. Reference: Svobodova, B et al. International Journal of Molecular Sciences 2023, 24 (11), 9124.

Disclosures: M. Horak: None. **J. Korabecny:** None. **O. Soukup:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.16/C108

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

Support: NRF Korea Grant/2021R1I1A3060435
NRF Korea Grant/2020R1F1A1076616
Chonnam National University Hospital Biomedical Research Institute/BCRI23041
Korea Institute for Advancement of Technology (KIAT)/P00320818
Chonnam National University/2024-1135-01

Title: The therapeutic effect of miR-937-3p by targeting NTN1 expression and regulating apoptosis on Ab-induced Alzheimer's disease model

Authors: J. CHOI[1], H. JEONG[1], J. HWANG[1], C. KIM[4], S. LEE[5], H.-H. CHO[2], B. KIM[3], H.-S. JEONG[1], *S. JANG[1];
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Abstract: The therapeutic effects of miR-937-3p by targeting NTN1 expression and regulating apoptosis on Aβ-induced Alzheimer's disease model
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AbstractMicroRNAs (miRNAs) are known to have multiple function to regulate of gene expression in various types of species. There are a few studies about the miRNAs to influence Alzheimer's Disease (AD) pathogenesis, however, the potential neuroprotective effects of miRNAs in AD, particularly by targeting neuronal markers, still remain unclear. We aimed to clarify the therapeutic and neuroprotective role of miR-937-3p in AD by regulating apoptotic signal. Our biological analysis confirmed the roles of miR-937-3p in neuronal protection and differentiation. So that, we selected a novel miR-937-3p and identified the target gene, NTN1, which is one of the regulators of axon guidance by qPCR analysis and luciferase assay. In addition, we observed a decrease in apoptosis levels induced by Aβ in SH-SY5Y cells upon treatment with a miR-937-3p inhibitor by FACS analysis. Similarly, western blotting analysis showed an increase in the expression of Mcl-1, an anti-apoptotic marker, with miR-937-3p inhibitor treatment in an *in vitro* AD model. Interestingly, the upregulation of pro-caspase 7, pro-caspase 3, and pro-PARP, which typically decrease as their cleaved forms increase, was increased with miR-937-3p inhibitor. Furthermore, the expression of neuronal markers such as NeuN, NFH, Tuj1, and MAP2 was enhanced with miR-937-3p inhibitor treatment in the *in vitro* AD model. In conclusion, our findings suggest that inhibition of miR-937-3p may play a therapeutic and neuroprotective role in AD by promoting NTN1 expression and repressing the apoptosis pathway.

Disclosures: J. Choi: None. **H. Jeong:** None. **J. Hwang:** None. **C. Kim:** None. **S. Lee:** None. **H. Cho:** None. **B. Kim:** None. **H. Jeong:** None. **S. Jang:** None.

Poster

PSTR449: Alzheimer's Disease and Related Dementias: *In Vitro* Models and Therapeutics

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR449.17/C109

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

Support: NIH Grant AG072587
NIH Grant AG062296

Title: Preclinical development of Alzheimer's disease immunotherapies using conformationally constrained β-strands and β-hairpins from Aβ and tau

Authors: *A. KREUTZER[1], J. ZHU[1], J. CARRERA PLANCARTE[2], S. RUTTENBERG[1], J. NOWICK[1];
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Abstract: Therapeutic strategies aimed at clearing or preventing the accumulation of Aβ and tau have dominated disease-modifying Alzheimer's disease (AD) drug development for decades, with monoclonal antibody (mAb) immunotherapies at the forefront of this effort. Anti-Aβ immunotherapies are now showing some promise in the clinic, leading to modest reductions in cognitive decline in AD patients. Tau immunotherapies have shown efficacy in AD mouse models, but have thus far failed to reduce cognitive decline in humans. The only modest reduction in cognitive decline elicited by anti-Aβ mAbs and the failure of anti-tau mAbs underscores the need for improved immunotherapies that lead to a greater reduction in cognitive decline in AD. High-resolution cryo-EM structures of tau and Aβ fibrils from AD brains have transformed our understanding of the molecular basis of AD and provide new disease-related molecular targets for combatting its underlying pathophysiology. These AD brain-derived tau and Aβ fibril structures provide the first opportunity for structure-based design of anti-tau and anti-Aβ mAbs against disease-related, structurally defined targets. mAbs that target disease-related conformations and assemblies of tau and Aβ offer the promise of improved efficacy. This talk presents the creation and study of antibodies designed to target disease-related conformations adopted by Aβ and tau. These antibodies were raised against peptide antigens that mimic β-hairpins of Aβ and oligomers formed by the β-hairpins, and β-strands formed by tau in AD brain-derived fibrils. Ex vivo immunohistochemical and biochemical studies in AD brain-tissue and cell-based studies were performed to characterize the antibodies. The antibodies raised against the Aβ-derived peptide antigens recognized Aβ plaques in AD brain tissue and in 5xFAD mouse brains and protected iPSC-derived human neurons from Aβ toxicity. Biochemical characterization of these Aβ-derived antibodies showed that the antibodies exhibit some selectivity for aggregated forms of Aβ. The antibodies raised against the tau-derived peptide antigens recognized tau neurofibrillary tangles in AD brain tissue and inhibited tau seeding in a cell-based tau biosensor assay. These findings demonstrate that antibodies raised against conformationally constrained β-hairpins and β-strands derived from Aβ and tau exhibit characteristics beneficial for AD immunotherapy, such as recognition of Aβ and tau pathology, protection against Aβ cytotoxicity, and inhibition of tau seeding. The study of these antibodies sets the stage for investigating their potential as AD immunotherapies.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.01/C110

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

Support: 1U01NS114144

Title: Analytical Validation of MSD S-PLEX Neurology Panel 1

Authors: *C. DEMOS[1], N. PADMANABHAN[1], R. E. COHEN[1], J. BROWN[1], T. GORHAM[1], J. MCBRIDE[1], S. SESAY[1], S. RIVERA VELEZ[2], A. BARNES[3], J. YANG[3], D. GRAHAM[3], A. EVERETT[3], C. CAMPBELL[1], A. MATHEW[1], M. STENGELIN[1], G. SIGAL[1], J. WOHLSTADTER[1];
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Abstract: Glial fibrillary acidic protein (GFAP), neurofilament light (Nf-L), and Tau are promising biomarkers for the research of neurological disorders and injuries such as hypoxic-ischemic encephalopathy (HIE) and Alzheimer's disease (AD). Detecting the low levels of these biomarkers in serum and plasma requires highly sensitive assays. Here, we report the characterization of a commercial, ultrasensitive, multiplexed immunoassay for GFAP, Nf-L and Tau, with the goal of analytically validating the panel for assessment of biomarker levels associated with HIE in infants.
The MSD S-PLEX Neurology Panel 1 kit uses ultrasensitive S-PLEX assay technology to simultaneously measure levels of GFAP, Nf-L, and Tau (total) in a 96-well plate format. Analytical validation was performed in a series of studies based in part on Clinical and Laboratory Standards Institute guidelines to evaluate precision, dilution linearity, spike recovery, interference screening and stability. Precision was assessed through a multi-site reproducibility study performed at MSD, Johns Hopkins University, and Johns Hopkins All Children's Hospital. Reagent stability was assessed through a two-year, real-time stability study.
The quantifiable range of the assay was 6.9-7,100 pg/mL for GFAP, 6.3-25,800 pg/mL for Nf-L, and 0.98-4,030 pg/mL for Tau. A set of 15 common interfering substances was screened, and none showed interference exceeding 18%. Dilution of spiked and HIE samples up to 256-fold recovered at 80-120% of the expected value for all analytes. Precision error calculated using 40 samples across 3 independent laboratories and 3 production lots of the panel (360 measurements) was 18.2% for GFAP, 20.8% for Nf-L, and 17.5% for Tau. These samples included adult and umbilical cord serum and plasma, challenge samples, and diseased samples with AD and other neurological diagnoses. Stability was measured with 20 plate runs per time point per lot at 12, 18, and 24 months; calculated drift was negligible, providing excellent shelf life for longer-term clinical studies.
The MSD S-PLEX Neurology Panel 1 kit provides an analytically validated tool for assessing human GFAP, Nf-L, and Tau. The kit is sufficiently sensitive to detect these analytes in normal serum and plasma, the reproducibility and stability can support large studies, and its dynamic range is capable of quantifying elevated levels found in HIE and other target neurological disorders.

Disclosures: C. Demos: A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **N. Padmanabhan:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **R.E. Cohen:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Brown:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **T. Gorham:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. McBride:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **S. Sesay:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **S. Rivera Velez:**

None. **A. barnes:** None. **J. Yang:** None. **D. Graham:** None. **A. Everett:** None. **C. Campbell:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **A. Mathew:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **M. Stengelin:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **G. Sigal:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Wohlstadter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Meso Scale Diagnostics, LLC.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.02/C111

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

Title: Longitudinal changes in blood-based biomarkers in at-risk, preclinical and early symptomatic neurodegenerative disease patients receiving precision preventive care

Authors: *C. M. JANNEY[1], P. SISSER[2], K. NIOTIS[3], A. SEIFAN[4], H. HRISTOV[3], S. HELFMAN[3], P. PARTHASARATHY[3], D. ANGERBAUER[3], C. SAPERIA[3], L. VALOIS[3], C. BRUBECK[3], J. A. MELENDEZ-HERENCIA[5], N. CLUTE-REINIG[3], J. LAKIS[3], H. HUBER[6], H. ZETTERBERG[6], R. ISAACSON[3];
[1]Parkinson's Res. and Educ. Fndn. (PAREF), Inst. for Neurodegenerative Dis. (IND) Florida, Boca Raton, FL; [2]Florida Atlantic Univ. Schmidt Col. of Med., Boca Raton, FL; [3]Inst. for Neurodegenerative Dis. (IND) Florida, Boca Raton, FL; [4]Inst. for Neurodegenerative Dis. (IND) Florida, BRONX, NY; [5]Memory Assessment Service, States of Jersey, Grouville, Jersey; [6]Dept. of Psychiatry and Neurochemistry, Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Despite the availability of a variety of interventions known to modify risk factors for neurodegenerative disease (NDD), non-invasive tools for measuring effectiveness of preventive care on pathological markers of disease are limited. Recent advances in blood-based biomarker technology also hold promise for monitoring response to preventative treatments. In the current study (N=15; male [n = 10], female [n= 5], mean age [60.2 (SD = 10.63)], APOE-Ɛ4 Non-Carrier [n = 2], APOE-Ɛ4 Heterozygous [n = 9], APOE-Ɛ4 Homozygous [n = 4]), individuals with an early stage clinical diagnosis of neurodegenerative disease (Dementia with Lewy Bodies (DLB) [n = 1], MCI due to AD [n = 3], Primary Age-related Tauopathy (PART) [n = 1]), preclinical individuals (Preclinical AD [n = 3], Preclinical DLB [n = 3]), and at-risk individuals (Normal at-risk [n = 6]) had plasma collected prior to receiving one or more preventive neurological interventions informed by precision medicine (Pre-intervention baseline). Interventions included lifestyle modification, desmosterol-sparing lipid management, GLP-1 agonist treatment, and hormone replacement therapy, among others. At one or more time points after receiving intervention, plasma was collected again. The most recent time point (Post-intervention timepoint) for each patient was used to determine plasma biomarker changes from pre-

intervention to post-intervention. Blood-based biomarkers included Boston Heart labs (Lipid Panel, Inflammation/Oxidation tests, Cardiac Muscle Function, Metabolic Panel, Fatty Acid Balance, Hormones, and Others); PrecivityAD C2N (Aβ42/40 Ratio); Quanterix SIMOA assays (Aβ42/40 Ratio, pTau217, Nfl, GFAP); and Alamar NULISA assays (Aβ42/40 Ratio, pTau217, Nfl, GFAP). Results indicated a significant improvement in ApoA-I ($p = 0.0038$), Trans Fatty Acid Index ($p = 0.0405$), C2N AB42/40 ($p = 0.0130$), and Quanterix ALZPath pTau217($p= 0.0063$) (Alamar NULISA results are pending). This is one of the first studies to show that 1) blood based biomarkers are a feasible method for screening for biomarkers related to NDD and monitoring NDD-related markers after risk-reduction treatment in humans, and 2) early, personalized, preventive neurological interventions targeting multiple risk factors can positively impact blood-based biomarkers of neurodegenerative diseases.

Disclosures: C.M. Janney: A. Employment/Salary (full or part-time):; Institute for Neurodegenerative Diseases (IND) Florida. **P. Sisser:** None. **K. Niotis:** None. **A. Seifan:** None. **H. Hristov:** None. **S. Helfman:** None. **P. Parthasarathy:** None. **D. Angerbauer:** None. **C. Saperia:** None. **L. Valois:** None. **C. Brubeck:** None. **J.A. Melendez-Herencia:** None. **N. Clute-Reinig:** None. **J. Lakis:** None. **H. Huber:** None. **H. Zetterberg:** None. **R. Isaacson:** None.

Poster

PSTR450: New Biomarkers for Alzheimer’s and Parkinson’s Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.03/C112

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

Support: CIHR

Title: Age-associated changes in circulating irisin and cathepsin B and their relationship with AD-related biomarkers

Authors: *T. HUNTER[1], N. M. LYRA E SILVA[2,3], T. RODY[5], G. B. DE FREITAS[3], J. ZHANG[2], J. J. HEISZ[6], B. MICHALSKI[7], M. FAHNESTOCK[7], F. DE FELICE[2,3,8,9,4]; [1]1Department of Biomed. and Mol. Sci., [2]Dept. of Biomed. and Mol. Sci., [3]Ctr. for Neurosci. Studies, [4]Dept. of Psychiatry, Queen's Univ., Kingston, ON, Canada; [5]Inst. of Med. Biochem. Leopoldo de Meis, Univ. Do Rio De Janeiro, Rio De Janeiro, Brazil; [6]Dept. of Kinesiology, [7]Dept. of Psychiatry and Behavioural Neurosciences, McMaster Univ., Hamilton, ON, Canada; [8]Inst. of Med. Biochem. Leopoldo de Meis, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [9]D’OR Inst. for Res. and Educ., Rio de Janeiro, Brazil

Abstract: Alzheimer’s disease (AD) is the leading cause of dementia in the elderly population. Exercise is widely proposed as an intervention to reduce the risk and progression of AD. Myokines are molecules secreted by skeletal muscle contraction and may be involved in the

effects promoted by exercise. Hence, it is crucial to establish relationships between circulating myokines, age, and AD-related biomarkers. Irisin and cathepsin B are two myokines previously implicated in AD. Our group has demonstrated that irisin mediates the beneficial effects of exercise on memory and that irisin may be a useful AD biomarker in cerebrospinal fluid. While the neuroprotective role of irisin has been well characterized, cathepsin B may contribute to both neuroprotection and neurodegeneration. In this study, we aim to determine the changes in serum irisin and cathepsin B in young (ages 18-29 years; 11 males/17 females) and elderly (ages 65-79 years; 8 males/9 females) individuals and their relationship to AD-related biomarkers. Irisin and cathepsin B were measured in serum using enzyme-linked immunosorbent assay. Results from unpaired, two-tailed t-tests showed that compared to young individuals, elderly individuals have significantly reduced levels of serum irisin ($t(29) = 4.997$, $p < .0001$) and elevated levels of cathepsin B ($t(45) = 5.943$, $p < .0001$). These changes were seen in both males and females. Phosphorylated-tau (p-tau)181 was measured in the serum using single-molecule array (Simoa). Serum cathepsin B levels showed a significant positive correlation with serum p-tau181 (Pearson $r(11) = .5594$, $p = .0468$). These age-associated changes in circulating myokines and their relationship with AD-related biomarkers may reveal more about the disease pathogenesis and potential targets for pharmacological and non-pharmacological interventions in AD.

Disclosures: T. Hunter: None. **N.M. Lyra E Silva:** None. **T. Rody:** None. **G.B. De Freitas:** None. **J. Zhang:** None. **J.J. Heisz:** None. **B. Michalski:** None. **M. Fahnestock:** None. **F. De Felice:** None.

Poster

PSTR450: New Biomarkers for Alzheimer’s and Parkinson’s Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.04/C113

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

Support: NIH U01 AG024904

Title: Towards understanding the role of perivascular spaces in Alzheimer's disease: associations with genetic, vascular and protein biomarkers

Authors: *S. TANG[1,2], D. TOSUN-TURGUT[1];
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Abstract: Motivation:
There is increasing evidence that cerebrovascular and glymphatic-related deficits may precede and influence Alzheimer’s disease (AD) pathology. In this study, we investigated the relationship between enlarged perivascular spaces (EPVS) as a measure of glymphatic clearance integrity, white matter hyperintensities (WMH) as a measure of cerebrovascular integrity, and AD ß-

amyloid (Aß) biomarkers and APOE ε4 genotype as a genetic risk for AD.
Methods:
Participants from ADNI-3 (N=915) who were diagnosed as cognitively unimpaired (CU) (N=515), mild cognitively impaired (MCI) (N=302), or AD dementia (N=98) were included. EPVS were segmented on 3T T1-weighted images using a novel fully-automated algorithm. WMH were segmented on 3T FLAIR images using the Lesion Segmentation Toolbox. Pairwise comparisons between EPVS and WMH metrics across diagnostic, APOE and Aß status groups were tested using Mann-Whitney U-tests. A generalized linear model (GLM) was used to model the relationship between EPVS and WMH in each condition. Age and sex were included as potential confounding factors, and data were transformed as needed.
Results:
EPVS count, volume, and WMH volume were greater in AD than in CU and MCI (all comparisons $p<0.05$). Those who were AB+ had higher EPVS count, volume and WMH volume compared to Aß- ($p<0.001$). Specifically, those who were CU and Aß+ had higher EPVS count, volume, and WMH volume than CU and Aß- ($p=0.007$, $p=0.02$, $p<0.001$). EPVS volume was greater in the ε4-carrier group than the ε4-noncarrier ($p=0.04$). A significant association was found between EPVS metrics and WMH volume ($R2=0.4$; $p<0.001$). MCI compared to CU presented a stronger EPVS count to WMH association ($p=0.02$). A stronger association was found between EPVS metrics and WMH volume in the Aß+ and ε4-carrier groups separately, and this pattern was sustained in the CU group. However, these differences were not statistically significant. There was a significant positive association between EPVS metrics and centiloid values ($R2=0.1$, $p<0.001$).
Conclusions:
We found that the association between measures of EPVS and WMH varies with different clinical stages of AD, Aß status, and AD genetic risk. This suggests that cerebrovascular and glymphatic-related deficits may interact and exacerbate in all clinical stages with varying degrees and timing. Untangling the relationship between these pathophysiological changes and their influence on AD progression will further our understanding of the etiology of AD and highlight potential modifiable risk factors.

Disclosures: S. Tang: None. **D. Tosun-Turgut:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.05/C114

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

Title: Detection of pTau217 in Alzheimer's disease tissue and biofluids using a newly developed monoclonal antibody

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Abstract: Phosphorylated tau have emerged as potential fluid-based biomarkers for Alzheimer's disease (AD) (1). Establishing a fluid-based biomarker, which measures analytes from patient cerebrospinal fluid (CSF) or plasma that associates with disease, would accelerate clinical research in treating this devastating neurodegenerative disease. Amongst several specific tau phosphorylation sites, phosphorylation at threonine 217 (pTau217) has emerged as a potential reliable biomarker, as levels of pTau217 increase in autosomal dominant AD patients (2) and may discriminate AD patients from non-AD patients compared to other tau phosphorylation sites (3,4). Measurement of fluid-based biomarkers largely leverage immuno-based technologies, which include enzyme-linked immunosorbent assay (ELISA) assays, immunoassays with electrochemiluminescence detection (ECL), single molecule arrays, and immunoprecipitation mass spectrometry (IP-MS). These assays require antibodies to the target protein of the highest specificity and sensitivity.

To improve on these immunoassays, we sought to develop a rabbit monoclonal antibody to pTau217. Screening of rabbit monoclonal antibody libraries identified a clone, E9Y4S, that exhibited properties specific to pTau217. Affinity and binding kinetics of E9Y4S using bio-layer interferometry (BLI) were measured and demonstrated significant advantages when compared to another on-market pTau217 antibody. By western, we detected bands consistent with tau from WT mice, absent in lambda phosphatase-treated tissue and tau KO brain lysates. The E9Y4S clone specifically detected phosphorylated tau 217 peptide without reactivity to the corresponding non-phosphorylated tau. Using the E9Y4S clone, we developed a sandwich ELISA-compatible antibody pair and plate able to detect pTau217 in rodent tissues as well as elevated pTau217 levels in human AD brain tissue compared to non-diseased controls. We then sought to determine the viability of E9Y4S to detect pTau217 in biofluids. We successfully used the pTau217 ELISA to detect elevated levels of pTau217 in plasma from the TauP301S transgenic mouse model compared to WT controls. Finally, E9Y4S, when paired with a total tau antibody, was able to distinguish between AD and non-AD in human CSF. Together, our data suggest the newly identified E9Y4S pTau217 monoclonal rabbit antibody is highly specific and sensitive to pTau217 and could be used in pair-based immunoassays to detect pTau217 in biofluids.

Disclosures: A.L. Aiello: A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc.. **L. Liu:** None. **D.E. Mulhern:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **T.C. Wiederhold:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **R.W. Cho:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc..

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.06/C115

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

Support: Dean's ASPIRE Grant, Johns Hopkins University
Albstein Research Scholarship, Johns Hopkins University

Title: Using novel cryptic ACTL6B antibody to detect TDP-43 loss of function

Authors: *M. J. CHEN[1], K. E. IRWIN[2], K. CHANG[3], K. E. BRAUNSTEIN[4], I. R. SINHA[2], J. C. TRONCOSO[5], J. P. LING[2], P. C. WONG[6];
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Abstract: The nuclear clearance and cytoplasmic aggregation of splicing repressor TAR DNA/RNA-binding protein-43 (TDP-43) occur in amyotrophic lateral sclerosis-frontotemporal dementia (ALS-FTD) and approximately 50% of Alzheimer's disease (AD) cases, driving neuron loss (Ling et.al., 2015; Meneses et.al., 2021; Neumann et.al., 2006; Cairns et.al., 2007). However, it is not clear how early such loss of function occurs in human disease as there is no method of detecting TDP-43 dysregulation in living individuals. Since the loss of TDP-43 leads to cryptic exon inclusion, we propose that cryptic exon-encoded peptides may be detected in patient biofluids to indicate TDP-43 loss of function. We developed antibodies against a TDP-43-dependent cryptic peptide within actin-like protein 6B (ACTL6B) and showed that cryptic ACTL6B is detectable in human brain neurons depleted of TDP-43. We also developed a sandwich ELISA for cryptic ACTL6B detection in biofluids.We characterized ACTL6B cryptic antibodies through protein blot analysis using TDP-43-knockdown (KD) SH-SY5Y neuroblastoma cell lysates. To test the antibody's sensitivity and specificity for cryptic ACTL6B in human brains, we used immunohistochemistry, immunofluorescence staining and BaseScope Assay on control, ALS, FTLD, and AD brain tissues. We then developed a Meso Scale Discovery (MSD) ELISA using our cryptic ACTL6B antibody.Cryptic ACTL6B monoclonal antibody demonstrated specificity for KD SH-SY5Y. Using this antibody, we detected ACTL6B signal in FTLD and AD, but not control, brain tissues. The cryptic ACTL6B staining colocalizes with neurons that display TDP-43 nuclear depletion. Using transfected SH-SY5Y cells to overexpress either cryptic or WT ACTL6B, the MDS ELISA was sensitive and specific for cryptic ACTL6B in transfected SH-SY5Y cells overexpressing cryptic compared to WT ACTL6B.Our findings provide evidence that our cryptic ACTL6B antibody is sensitive and specific for the ACTL6B cryptic peptide in both SH-SY5Y cells and human brain tissues. This antibody could be used to determine TDP-43 nuclear clearance/loss of function upon pathological staining, which could be a more sensitive approach than detection of cytoplasmic phosphorylated TDP-43. Our novel MSD ELISA for cryptic ACTL6B may be used in the future as a fluid biomarker of TDP-43 dysfunction.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.07/C116

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

Support: NIH Grant R01AG062006

Title: Anxiety, Odor Memory, and Apolipoprotein-E ε4 Allele: Exploring Early Biomarkers of Alzheimer's Disease Risk

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Abstract: The relationship between anxiety and odor memory, particularly in the presence of Alzheimer's disease (AD) biological risk factors such as the Apolipoprotein-E (ApoE) ε4 allele, is not well understood. Anxiety is associated with impaired memory in preclinical AD (Becker et al., 2018), and impaired odor memory has been identified as a risk factor for AD (Murphy, 2019). This study draws from both findings to examine whether a relationship exists between anxiety and odor memory in young and old age groups. Additionally, we examined whether the impact of anxiety on odor memory would be moderated by Apoe ε4 carrier status, such that at a given anxiety level, ε4 carriers would have weaker odor memory than ε4 noncarriers. Young adults aged 18-26 (n= 27) and older adults aged 62-84 (n= 21) completed the State Trait Anxiety Inventory-Trait Version (STAI-T) and the California Odor Learning Test (COLT), an olfactory analogue to the California Verbal Learning Test (Murphy, Nordin, & Acosta, 1997; Frank & Murphy, 2020), as well as genotyping for the presence of an ε4 allele. The impact of anxiety and the interaction of ε4-status and anxiety on odor memory, while controlling for sex, were assessed using separate multiple linear regression analyses in young and old age groups. Only in the young group, elevated anxiety significantly impacted odor memory performance, such that elevated anxiety was associated with greater trial 1-5 total recall (β= 1.582, p = .007), long-delay free recall (β= 1.626, p = .006),long-delay cued recall (β= 1.550, p = .008), short-delay free recall (β= 1.677, p = .003), and short-delay cued recall scores (β= 1.632, p = .005). A significant interaction effect between ε4-status and anxiety on odor memory performance was also found only in the young group, such that higher anxiety was associated with lesser trial 1-5 total recall (β=-2.223, p = .017), long-delay free recall (β= -2.289, p = .014), long-delay cued recall (β= -2.224, p = .017), short-delay free recall (β= -2.248, p = .013), and short-delay cued recall scores (β= -2.280, p = .012) among ε4 carriers and better odor memory performance across all measures among ε4 noncarriers. The results imply that anxiety weakens odor memory among young adult Apoe ε4 carriers yet strengthens odor memory performance among young adult Apoe ε4 noncarriers, indicating an interplay between anxiety, genetic predisposition, and odor memory that warrants further investigation in understanding early biomarkers of Alzheimer's disease risk.
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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.08/C117

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

Support: NIH R01AG079241
Morton Plant Mease Foundation nonprofit

Title: The Relationship between Subjective Visual Impairment and Domain-Specific Cognitive Performance in Cognitively Normal Older Adults and MCI Patients.

Authors: *J. SERGIO[1], A. DUBOIS[1], L. THOMPSON[2], A. PRICE[1], M. STRADTMAN[3], P. SNYDER[1,4], J. ALBER[4];
[1]Univ. of Rhode Island, Kingston, RI; [2]Psychiatry & Human Behavior, [3]Brown Univ., Providence, RI; [4]BPS, Univ. of Rhode Island Interdisciplinary Neurosci. Program, Kingston, RI

Abstract: Motivation/problem statement: Age is the greatest risk factor for self-reported visual impairment (VI) and Alzheimer's Disease (AD). While prior studies demonstrate associations between VI and cognitive screening measures in older adults, the relationship between VI and domain specific cognition remains unexplored. We examined the relationship between subjective VI and executive function, attention, visuospatial construction, episodic memory, and processing speed. Methods/ approach: Participants were age-matched older adults aged 55-80: 58 cognitively unimpaired (CU) (MoCA>=26, CDR=0), divided into high-risk (APOE E4 carriers) and low-risk (APOE E4 non-carriers) for AD, and 19 MCI patients (MoCA>19, <24, CDR=.5). Subjective VI was measured with the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Cognitive assessment included: MoCA, CDR, Digit Symbol Substitution Test (DSST), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Free and Cued Selective Reminding Test (FCSRT). Pearson's correlations were used to examine the association between NEI-VFQ composite with cognitive scores. Linear regressions were run to examine whether subjective visual impairment predicted cognitive test results of significant correlations, and secondarily whether cognitive performance predicted subjective visual impairment. Results: There were significant correlations between scores on the composite NEI-VFQ and both the DSST and RBANS visuospatial sub-scale in the CU group, and between NEI-VFQ composite scores and the DSST and RBANS delayed memory subscale in the high-risk group ($p<.05$). Higher NEI VFQ scores trended toward predicting lower RBANS delayed memory scores, while both the RBANS delayed memory and DSST significantly predicted

scores on the NEI VFQ composite in the high-risk group. Conclusions/implications: Attention, executive function, and visuospatial performance were related to subjective VI in CU older adults, and after breaking the CU group down by AD risk, these associations remained in only the high-risk group. No significant relationships were observed between subjective VI and cognition in the patient group, suggesting that subjective VI changes which affect domain-specific cognition may peak pre-symptomatically. Subjective VI and cognitive performance associations indicated a bi-directional relationship. Subjective measures of VI may serve as a tool in early detection of cognitive impairment. Longitudinal studies are ongoing to examine the predictive value of subjective VI on cognitive impairment.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.09/C118

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

Support: NIH grant R01AG063857

Title: Working memory processing relates to plasma biomarkers in cognitively healthy individuals

Authors: *V. LEONG[1], C. MOLLOY[1], X. WU[2], D. SIMMONS[2], N. ASTRAEA[2], A. N. FONTEH[3], X. ARAKAKI[1];
[1]Neurosci., [2]Analytical Biochem. Core, Huntington Med. Res. Inst., Pasadena, CA; [3]Mol. Neurol Program, Huntington Med. Res. Int, Pasadena, CA

Abstract: Background: Working memory (WM) is a core executive function that transiently stores and manipulates cognitive information in real time. Alpha Event-Related Desynchronization (ERD) from analysis of electroencephalogram (EEG) reflects WM processing and is related to memory storage, "neural efficiency," and WM capacity. However, there is limited knowledge of WM processing and performance in Cognitively Healthy (CH) participants. To contribute to this knowledge, we studied the relationship between alpha ERD, AD-related plasma biomarkers, and behavioral performance in CH participants who underwent a WM task. **Methods:** Cognitively healthy (CH) older participants (n=32) performed an N-back working memory test. EEG was recorded during 0-back (N0) and 2-back (N2) testing to monitor alpha desynchronization, where participants were shown a series of individual letters and asked to recall whether the letter presented was identical to the letter presented 0 or 2 letters back, respectively. We correlated alpha desynchronization at brain regions (frontal-F, central-C, parietal-P, left temporal-LT, right temporal-RT, occipital-O) to blood plasma (phosphorylated

tau 217, neurofilament light chain protein, and glial fibrillary acidic protein), response accuracy, and response timings using Spearman's correlations. **Results:** Within CH participants, there was a positive correlation between phosphorylated tau 217 (ptau217) and C, P, and LT alpha ERD (r=0.38-0.40, p=0.024-0.034) during 0-back testing. Participants also presented a positive correlation between ptau217 and RT alpha ERD (r=0.39, p=0.026) during 2-back testing. Both WM task paradigms revealed similar negative correlations between task response accuracies and ptau217 concentrations (r=-0.45, p=0.009 and r= -0.38, p=0.033). Neurofilament light protein (Nfl) and glial fibrillary acidic protein (GFAP) positively correlated with 0-back response times but negatively correlated with 2-back response accuracies (r=0.37-0.39, p=0.028-0.040 and r= -0.47, p=0.006-0.007, respectively). **Conclusion:** Analysis shows CH participants expressed less negative alpha ERD (less brain activation) with greater ptau217 concentrations during both working memory testing. Additional biomarkers, namely Nfl and GFAP, also modulate response behavior depending on the WM task conditions. These pilot analyses provide a rationale for fluid biomarkers as a potential mechanism underlying cognitive functioning.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.10/C119

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

Support: County Contract, Department of Mental Health & Office for the Aging (Rockland County, NY)

Title: Effect of Cognitive Reserve on Plasma Biomarkers of Alzheimer's Disease in Non-Demented Elderly

Authors: *C. REICHERT PLASKA[1,2], D. BRUNO[3], S. LEE[1,2], G. CRYSTAL NOVI[4,1], A. OREFICE[1], H. ZETTERBERG[5,6,7,8,9], K. BLENNOW[7,8,10,11], N. POMARA[1,2];
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Abstract: Education, a proxy for cognitive reserve (CR), has long been accepted as a protective factor against cognitive decline related to Alzheimer's disease (AD). In both normal and impaired elderly, higher CR is associated with less decline, even with notable AD pathology, including amyloid and tau. The relationship between CR and plasma AD biomarkers is unknown, so we examined this in nondemented elderly. Additionally, we examined whether the association of plasma AD biomarkers with cognitive performance is moderated by CR. We hypothesized that higher CR would have lower AD-risk blood biomarkers, and better cognitive performance. Cognitively unimpaired participants (n=530; Aged 50-85, MMSE=24+) recruited as part of the Memory Evaluation Research Initiative, completed a cognitive battery, including the Auditory Learning Verbal Test (AVLT) and Trail Making B test (TMTB). Plasma Aβ42, Aβ40, and Ptau231 concentrations were measured using Simoa assay. Plasma Aβ42/Aβ40 and Ptau/Aβ42 were calculated. While plasma Aβ42/Aβ40 and Ptau/Aβ42 may be equally predictive of increased brain Aβ burden, they may represent different stages of AD pathology; thus, both indices were used as outcomes. Years of education were used as a measure of CR: Low (CR-L; 12 years or less), Moderate (CR-M; 13-16), High (CR-H; 17 or more). We examined the effect of CR and *APOE* ε4 status on the plasma indices (Two-way ANOVA in SPSS), which was not significant. One-way ANOVA examined the effect of CR on plasma indices, which revealed a significant effect f =3.54 (p=0.030) on Aβ42/Aβ40. From Bonferroni post-hoc comparison, CR-L had lower Aβ42/Aβ40 than CR-H. A trend with CR-L and higher Ptau/Aβ42, than CR-H, p=0.057 was also found. PROCESS was used for a moderation analysis between plasma indices and cognition, with CR as the moderator. Moderation analyses showed that CR moderated the relationship between Ptau/Aβ42, not Aβ42/Aβ40, and AVLT delayed (CR-L vs -M: b=1.84, SE=0.58, p=0.001 and CR-M vs -H: b=2.70, SE = 0.58, p< 0.01), and total recall (CR-L vs -M: b=5.27, SE=1.71, p=0.002 and CR-M vs -H: b=8.64, SE=1.72, p< 0.01), as well as TMTB (CR-L vs -M: b = -27.82, SE = 9.62, p=0.004 and CR-M vs -H: b = -42.23, SE = 9.59, p< 0.01). Thus, the negative effects of Ptau/Abeta42 on cognitive performance seem to be mitigated by CR. Our results suggest that, in non-demented elderly, lower CR is associated with lower Aβ42/Aβ40 and higher Ptau/Aβ42 consistent with increased brain Aβ burden. In addition, CR also moderated the relationship between plasma Ptau/Aβ42, but not Aβ42/Aβ40, and cognition. Future studies should determine if low CR is associated with an accentuation of brain Aβ and tau pathology in nondemented older adults.

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Poster

PSTR450: New Biomarkers for Alzheimer’s and Parkinson’s Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.11/C120

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

Title: Independent effects of regional white matter hyperintensities and amyloid on domain-specific cognition and progression to dementia

Authors: *C. CHOO[1], C. TAN[2,3];
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Abstract: Global white matter hyperintensities (WMHs) and cerebral β-amyloid (Aβ) have been characterized as clinically significant biomarkers associated with greater cognitive decline and incidence of Alzheimer's Disease (AD) dementia. However, it remains unclear how their regional manifestations independently contribute to domain-specific cognition and AD dementia onset. In the current study, 200 cognitively normal (CN) (CDR = 0) and 523 individuals with mild cognitive impairment (MCI) (CDR = 0.5) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were investigated. We first quantified regional WMHs and Aβ accumulation in the four major lobes of the cerebral cortex (frontal, parietal, temporal, occipital). Using multiple regressions, we evaluated diagnostic group differences in regional WMHs independent of the corresponding regional Aβ. Next, we investigated the independent effects of both regional pathologies on four different domains of cognition (memory, executive function, language, visuospatial function). Lastly, using Cox proportional hazard models, we determined the independent contributions of both regional WMHs and Aβ on progression to AD dementia. Compared to CN individuals, we found that individuals with MCI exhibited increased WMHs in the parietal (p=.026) and occipital (p=.006) lobes, independent of the corresponding regional Aβ. Additionally, we show that in CN individuals, only increased WMHs in the parietal (p=.038) and temporal (p=.025) regions were independently associated with poorer executive function beyond regional Aβ accumulation. Whereas in MCI individuals, increased Aβ accumulation in all four lobes were associated with poorer memory (ps<.001), executive function (ps<.01), and language abilities (ps<.05), independent of regional WMHs. No associations of regional WMHs and Aβ with visuospatial function were observed for both CN and MCI groups. Lastly, we found that increased WMHs in the occipital lobes (p=.001) and Aβ in all four lobes (ps<.001) independently predicted progression to AD dementia in non-demented (CN & MCI) and in MCI individuals alone. These findings illustrate the presence of independent contributions of both regional cerebrovascular and Aβ pathologies in AD that may shift in a disease-stage dependent manner. Temporo-parietal WMHs may drive early decline in executive function independent of regional Aβ, while occipital WMHs play a critical role in disease progression to AD dementia beyond regional Aβ. Taken together, our results highlight the importance of understanding the complex interplay of regional WMHs and Aβ on domain-specific cognitive and clinical decline.

Disclosures: C. Choo: None. **C. Tan:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.12/C121

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

Support: Synaps DX

Title: Dynamic Diagnosis of Alzheimer's Disease Based on Positive and Negative Autopsy-Confirmed Gold Standard Trends

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Abstract: When used with living cells, the accuracy and reliability of biomarkers are critical for diagnosing various diseases. Pre-experimental cell status and culture media, such as fetal bovine serum (FBS), can significantly impact the results of biomarkers. It is imperative to understand the conditions that govern these two trends. In previous studies, the Morphometric Imaging (MI) Alzheimer's disease (AD) biomarker has been successfully tested on forty-six gold-standard autopsy-validated samples after establishing the cutoff as 95 percentiles on twenty-seven healthy control samples. Here, we propose a dynamic solution to address the impact of pre-experimental cell density and FBS on MI. Our novel diagnostic method uses a dynamic diagnosis of Alzheimer's disease based on positive and negative autopsy-confirmed gold-standard linear trends. We tested this method on twenty-five ADs and seven non-AD dementia gold-standard autopsy-validated samples, which showed that it improves the accuracy of the MI biomarker by accounting for the dynamic nature of the linear trends when changing the FBS. The theoretical framework developed for the study demonstrates the linear laws that govern MI's measure on the natural log of pre-experimental cell density. It also shows the linearity in the slope-intercept plane for different FBSs (R^2=0.997), the FBS lot equivalence for MI biomarker, the logarithmic law allowing ranking for different FBSs(R^2=0.927), and the parabolic law(R^2=1.000) directly relating to the MI's upper detection limit. Our analysis is general and applicable to other biomarkers using living cells and linear input-output dependence on one characteristic, which a second trait impacts. This dynamic method for biomarker testing emphasizes the importance of understanding the laws that govern pre-experimental cell characteristics for consistent and reliable results. With this method, we can ensure that the diagnosis and treatment of diseases are accurate and effective, providing patients with the best possible care.

Disclosures: F.V. Chirila: None. **D. Alkon:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.13/C122

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

Support: NIH P01AG078116-01
NIH P30 AG028383
NIH UL1TR001998

Title: Astrocyte Reactivity and Interleukin Biomarkers Link with Regional Brain Thickness and Volumes in Older Adults

Authors: *M. F. CLARK[1], Y. KATSUMATA[2,3], X. WU[2,3], D. K. POWELL[4], A. H. ANDERSEN[5], G. A. JICHA[4,3], T. L. SUDDUTH LEE[6], D. M. WILCOCK[7], C. M. NORRIS[8], Y. JIANG[9];
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Abstract: Background Medial temporal and parietal atrophy in the brain are associated with preclinical Alzheimer's Disease and vascular diseases. Further, astrocyte reactivity contributes to vascular/AD diseases. The plasma immune biomarkers GFAP, IL-6, and IL-10 which are associated with Astrocyte reactivity in the brain. Leveraging UK-ADRC neuroimaging and biomarkers data, we test the hypotheses that increased GFAP (Astrocyte reactivity) and IL-6 mediated inflammatory responses are associated with reduced brain thickness and regional volumes.
Methods34 (18 women) cognitively intact volunteers, and 3 (1 woman) mild-cognitively impaired volunteers, average age 79 (SD= 8.53) years old, from UK-ADRC longitudinal cohort participated. Thickness and Volume was assessed for each participant using Magnetic Resonance Imaging and vascular/AD plasma markers were collected and measured. **Results**We observed increased GFAP correlates with thinner cortical thickness in the lh/rh inferior (-0.416/-0.343), superior, and transverse temporal area (-0.321/-0.255, -0.258/-0.286), and smaller transverse temporal volume (-0.262, -0.286). The volume of both bilateral accumbens areas showed moderate negative correlations with both GFAP (-0.539, -0.462) and IL6(-0.345, -0.313). In contrast, IL-10 biomarker positively correlates with bilateral inferior parietal (IP) volume, right IP thickness, left superior parietal and right paracentral volume.
ConclusionsResults show the negative correlation of GFAP&IL6 in superior and transverse temporal regions indicate that astrocyte activity plays a key role in the neuroinflammatory process as neurodegenerative process. In comparison, the positive correlation with IL-10 seen in parietal cortices, suggesting the anti-inflammatory property of this cytokine may be serving as a compensatory response to similar processes of atrophy.

Disclosures: M.F. Clark: None. **Y. Katsumata:** None. **X. Wu:** None. **D.K. Powell:** None. **A.H. Andersen:** None. **G.A. Jicha:** None. **T.L. Sudduth Lee:** None. **D.M. Wilcock:** None. **C.M. Norris:** None. **Y. Jiang:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.14/C123

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

Support: NIH Grant AG076129

Title: Age and genetic background modulate the effect of Alzheimer's Disease on sleep.

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Abstract: BACKGROUND: Alzheimer's Disease (AD) is known to contribute towards changes to sleep, including decreased sleep duration and increased sleep fragmentation. While significant advances have been made in characterizing these changes, the contribution of individual genetic makeup on the initiation and progression of AD-related sleep dysfunction and pathogenesis is yet unknown. As such, we decided to use a forward genetic approach to identify genes controlling sleep in AD in a panel of genetically diverse mice (AD-BXDs). **METHODS:** Female mice from 47 strains in the AD-BXD panel carrying the 5xFAD transgene (n = 214) and non-transgenic littermate controls (n = 216) completed sleep testing in the PiezoSleep Tracking System at 6 and 14 months of age. The percent of time spent sleeping was calculated over 4 testing days by automated sleep/wake scoring. After sleep phenotyping, animals were tested for learning and memory functions using contextual fear conditioning (CFC) at both ages - 6 and 14 months. **RESULTS:** At mid-life, non-transgenic (Ntg) mice sleep more over a 24-hour period than their 5xFAD and 6-month Ntg counterparts. This difference is particularly enhanced in the dark (active) phase, where the difference in sleep quantity between Ntg and 5xFAD animals is magnified by increased sleep in Ntg animals with age and a significant decrease in sleep in 5xFAD carrying animals with age. Interestingly, during the light (inactive) phase, 5xFAD animals slept more than non-transgenic counterparts at both 6 and 14 months of age. Heritability estimates for percent time sleeping over 24 hours, the 12-hour light period, and 12-hour dark period at 6 and 14 months of age were between 0.64-0.76 for both non-transgenic and 5xFAD animals, suggesting that genetic background may largely explain the observed changes. **CONCLUSION:** Genetic background modulates the effect of AD and age on sleep in the AD-BXD panel. Since sleep is vital for memory consolidation, future work will aim to map the genes modifying sleep in AD, and identifying the mechanisms through which sleep causally influences cognitive decline in AD and age-related dementias.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.15/C124

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

Support: NSF Grant #1848440
NIH UG3/UH3
University of Notre Dame Science of Wellness Initiative Seed Grant

Title: Neural Correlates of Cognitive Decline: Linking EEG Patterns in Working Memory Updating Tasks to Alzheimer's Disease Biomarkers

Authors: *C. XU[1], J. FRAGETTA[1], C.-M. CHAO[2], Z. XIE[3], D. HENRECKSON[4], N. S. ROSE[5];
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Abstract: Alzheimer's disease (AD) presents a significant public health challenge, necessitating reliable biomarkers for early detection and monitoring. Declines in working memory (WM) are common in healthy aging and especially in AD patients. This study investigates the relationship between neural measures of WM representations and updating processes, behavioral performance, and ADRD biomarkers in healthy older adults (N=47, Mage=70.68±7.35). Participants performed 1- and 2-back tasks with scene, object, and face memoranda during EEG recording. Blood-plasma assays provided participants' APOE allele status, a gene associated with AD risk, and Alzheimer probability score (APS) via measures of β-amyloid and phosphorylated-tau deposition. Other AD biomarkers include age, neurocognitive function (NIH Cognition Toolbox), aging signatures and indicators of cortical thinning (pADi). Machine learning classifiers were trained to decode the stimulus category during the delay period from power in the alpha, beta, theta and low-gamma frequencies. Higher decoding accuracy in alpha and theta frequencies was negatively correlated with age, even after controlling for behavioral performance of accuracy and RT. Additionally, low-gamma decoding accuracy was negatively correlated with APS. These results indicate that decoding accuracy in these frequencies is associated with age and APS, underscoring their potential as significant biomarkers independent of direct task performance. Behavior and neural indices of WM updating were also strong predictors of neurocognitive functions.In the 2-back task, the memoranda presented prior to the current item (n-1) is passively maintained in WM, whereas the memoranda presented two items before (n-2) is actively maintained. Results showed that RT in 1-back task and delay-period decoding accuracy in beta frequency for active items (n-2) in 2-back task were positively correlated with fluid intelligence. Decoding accuracy in beta frequency for passive (n-1) items in 2-back tasks were negatively associated with executive function. No significant association was found between measures of WM updating and aging signatures or pADi. Overall, our results highlight the importance of EEG-based neural decoding and behavioral measurement of WM

updating tasks in identifying early biomarkers of ADRD. These findings advance our understanding of the neurocognitive declines associated with aging and Alzheimer's disease and offer promising avenues for early detection and outcome measures to assess the efficacy of interventions.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.16/C125

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

Support: NIH R01AG422460
NIH R01AG420690

Title: Brain-derived tau oligomers in plasma brain-derived extracellular vesicles: a potential predictive biomarker for Alzheimer's disease.

Authors: *M. MARCATTI, W.-R. ZHANG, R. KAYED, G. TAGLIALATELA;
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Abstract: Alzheimer's disease (AD) represents one of the most prevalent forms of dementia worldwide. Therefore, it is crucial to establish specific predictive biomarkers to identify individuals with a high risk of developing AD, facilitating early treatment initiation during the preclinical stage. Recent investigations have focused on blood-based biomarkers, such as plasma brain-derived extracellular vesicles (pl-BDEVs) content, to detect alterations within the central nervous system (CNS). Although blood-based biomarkers for amyloid proteins (Aβ42/Aβ40 peptide, tau, and phosphorylated tau) demonstrate promising diagnostic accuracy and correlation with cerebrospinal fluid (CSF) and neuroimaging biomarkers in AD, the urgency of identifying predictive biomarkers remains essential. Blood total-tau primarily originates from non-brain sources, underscoring the importance of analyzing brain-derived tau (BDT) in pl-BDEVs as an AD and other neurodegenerative diseases biomarker. Longitudinal studies, which involve collecting repeated samples from a single patient over time, possess the potential to identify specific biomarker patterns during the preclinical stage of individuals who may develop AD. However, investigations have yet to focus on the role of oligomers, the most toxic species in AD. In this study, we enriched pl-BDEVs from CNS cell types (neurons, microglia, astrocytes, oligodendrocytes) from plasma samples longitudinally collected from participants enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC), who were initially cognitively normal or displayed mild cognitive impairment (MCI), and later either progressed to AD (termed "converters") or remained cognitively normal/MCI (termed "non-converters"). We evaluated the

isolated pl-BDEVs by nanoparticle tracking analysis (size, number, and distribution), and western blot (expression of extracellular vesicles markers: CD63, CD9, CD81). Moreover, we demonstrated the successful detection of brain-derived toxic tau oligomers (BDTOs) in pl-BDEVs derived from plasma samples. Western blot, immunocharacterization, and proteinase K digestion served as preliminary analyses to characterize these BDTOs. This study addresses the need for predictive AD biomarkers by exploring previously unexplored BDTOs conformers in pl-BDEVs. Discovering distinct BDTOs in peripheral brain derived extracellular vesicles could enable preclinical forecasting and advance early-stage AD treatments.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.17/C126

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

Support: NIH/NIA 2R01 AG053555

Title: Delineating the Relationship Between Plasma Biomarkers and Brain Amyloid Pathology In Preclinical Alzheimer's Disease

Authors: *R. WEERACKOON[1], S. KIM[1], E. A. THOMAS[2], R. MALHAS[1], M. MAPSTONE[3], J. N. ADAMS[4], L. TAYLOR[5], A. HARRIS[1], L. TRONDSEN[6], M. A. YASSA[7]; [1]Univ. of California Irvine, Irvine, CA; [2]Epidemiology and Biostatistics, Univ. of California, Irvine, Irvine, CA; [3]Univ. of California, Irvine, Irvine, CA; [4]UC Irvine, Irvine, CA; [5]Dept. of Neurobio. and Behavior and Ctr. for the Neurobio. of Learning and Memory, Univ. of California, Irvine, Irvine, CA; [6]Neurobio. and Behavior, UC Irvine, Irvine, CA; [7]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Over six million Americans are diagnosed with Alzheimer's disease (AD). By 2050, this number is projected to nearly triple to 16 million. Mitigating this rise necessitates establishing quantifiable preclinical indicators present prior to symptom manifestation. Brain amyloid-beta (Aβ) burden - a hallmark of AD pathology - is a principal preclinical indicator. Unfortunately, accessing this diagnostic currently requires either an expensive PET scan or a highly invasive spinal tap procedure. Fluid biomarkers, measured through blood or saliva samples, proffer a more accessible alternative. Identifying which fluid biomarkers correlate most closely with brain Aβ levels can help establish vital preclinical AD indicators and contribute to early risk assessment. In this study, plasma samples were collected from a cohort of 69 cognitively normal adults (40 female, aged 60-86, average age 70) enrolled in the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study at the University of California, Irvine, and run on the Quanterix Simoa platform. Brain Aβ was measured with 18F-

florbetapir-PET, using the mean SUVR of a cortical composite region as an indicator of global Aβ burden. Aβ positivity was defined as > 1.11 cortical composite SUVR. Relationships between individual biomarkers and Aβ-PET uptake were evaluated through linear regression analysis, and a Random Forest Classification machine learning model, which incorporated covariates like age, sex, and education, was created to determine which combination of plasma biomarkers best predicted Aβ status. We found that, while Aβ-PET does not correlate with cerebrovascular integrity markers like VEGF, TGFβ, and PDGF-BB, it does increase significantly with AD pathological markers like pTau-217 (R=0.425) and pTau-181 (R=0.262), and GFAP (R=0.554). Moreover, the latter exhibited above-chance accuracy in predicting Aβ status (AUC=0.68). In all, these results suggest that specific plasma biomarkers can be used in the future to reliably estimate one's brain amyloid levels and, by extension, their preliminary risk for developing AD.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.18/C127

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

Support: American Heart Association
NIH R01 Grant NS119593
NIH RO1 Grant MH125429
Washington Research Foundation

Title: Identifying dynamic functional connectivity biomarkers for Alzheimer's disease detection using graph diffusion autoregression

Authors: *F. SCHWOCK[1], D. NORDGREN[1], L. ATLAS[1], H. JAHANIAN[2], A. YAZDAN-SHAHMORAD[3];
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Abstract: Recent advances in Alzheimer's disease (AD) treatments, such as the introduction of amyloid beta (Aβ) lowering drugs like Lecanemab, offer potential to slow or reverse the disease's progression. However, the effectiveness of these treatments is largely limited to the early, pre-clinical stages of AD, which can begin decades before symptoms appear. This necessitates the development of biomarkers that can detect the earliest signs of Aβ accumulation and other pathological changes in the brain during this pre-clinical phase. Current biomarkers do not fully

meet these clinical needs, highlighting a pressing need for new, readily accessible, and noninvasive biomarkers that can identify AD at this critical early stage. An emerging direction is to use functional magnetic resonance imaging (fMRI) and extract functional connectivity (FC) features from resting state brain recordings to distinguish between AD patients and healthy control subjects. However, most current approaches rely on static measures of network connectivity thereby neglecting dynamics that may be informative of the state of the disease. To infer dynamic interactions between brain regions, we have recently developed the graph diffusion autoregressive (GDAR) model, which can estimate the dynamic flow of information between brain regions from distributed recordings of neural activity. In this framework, the propagation of neural activity is modeled via a network diffusion process on top of a brain graph and the model produces a time varying communication signal on the graph edges that can be used as a biomarker for the detection of neurological disorders. To validate the model, we have applied it to fMRI recordings from healthy subjects showing that it can accurately predict future neural activity and produce communication signals that are stable within and across subjects. We then applied the GDAR model to fMRI data recorded from AD patients during different disease stages to characterize changes in dynamic network communication as the disease progresses. We believe that this model will provide an important step towards identifying new biomarkers for the early detection of AD and other neurological disorders.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.19/C128

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

Support: R01AG063857

Title: Functional Connectivity in Cognitively Healthy Individuals with Low and High Plasma P-tau217 differs during an interference task

Authors: *A. MOHAMMED[1], N. ASTRAEA[2], C. MOLLOY[1], V. LEONG[1], X. WU[2], D. SIMMONS[2], A. N. FONTEH[3], X. ARAKAKI[1];
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Abstract: Introduction: Plasma phosphorylated tau has emerged as a reliable metric to assess Alzheimer's disease (AD) progression. Specifically, in prior research, elevated plasma p-tau217 demonstrated dynamic longitudinal correlation with various domains of cognition and cortical atrophy. However, the relationship between plasma p-tau217 levels and functional brain

connectivity (FC) in cognitively healthy (CH) individuals remains largely unexplored. **Method**: Electroencephalogram (EEG) data were recorded from 50 CH participants using a 24-sensor headset (Wearable Sensing, DSI-24) in resting and Stroop interference test. During the test, participants were presented with color words one at a time when ink color of the color word matched (congruent) or did not match (incongruent). Participants were asked to respond to the ink color, not the color word. Blood samples were collected for the same cohort to analyze plasma p-tau217 by electrochemiluminescence (MSD SQ 120). Aging participants were classified into two groups based on the median level of p-tau217 for this population, including n=25 low p-tau217 levels (age: 74.6 ± 8.4 years; ptau217 < 4.3 pg/mL) and n=25 high p-tau217 levels (age: 73.7± 6.3 years; ptau217 > 4.3pg/mL). We calculated FC at each electrode using Partial Directed Coherence (PDC) to evaluate the association between FC and p-tau217. In this exploratory analysis, a non-parametric t-test was used with no multiple correction. **Results**: Our pilot study revealed distinct FC patterns between the two groups during cognitive processing. Compared to the low p-tau217 group during congruent Stroop trials, the high p-tau217 group exhibited decreased temporal FC and increased FC around the posterior cingulate cortex. During incongruent Stroop trials, the high p-tau217 group showed reduced frontal-temporal FC compared to the low p-tau217 group (Figure 1). No differences in FC were observed during the resting state between the two groups. **Discussion**: These findings underscore plasma p-tau217's influence in the biomolecular mechanism underlying early changes in FC during interference processing. The differential FC patterns revealed by cognitive challenge observed between the two groups may potentially aid in detecting AD pathology in CH individuals.

Disclosures: A. Mohammed: None. **N. Astraea:** None. **C. Molloy:** None. **V. Leong:** None. **X. Wu:** None. **D. Simmons:** None. **A.N. Fonteh:** None. **X. Arakaki:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

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Title: Synaptic and neuronal degeneration in the retina of MCI and AD patients are linked to retinal and brain AD pathology and cognitive status

Authors: *E. K. ROBINSON[1], A. RENTSENDORJ[1], D.-T. FUCHS[1], J.-P. S. VIT[2], B. GAIRE[1], M. R. DAVIS[1], O. JALLOW[1], L. SCHNEIDER[3], Y. KORONYO[1], M. KORONYO-HAMAOUI[1,4,5];
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Abstract: Alzheimer's disease (AD) is the foremost cause of global dementia, also characterized by retinal changes involving Aβ, hyperphosphorylated-tau (p-tau), neuronal degeneration, and tissue atrophy. While synaptic loss is an early predictor of cognitive decline in AD, its occurrence in the AD retina remains unknown. Furthermore, mitochondrial-driven reactive oxygen species (ROS) production, linked to synaptic dysfunction and common to various neurodegenerative conditions, remains unstudied in the AD retina. This study explores retinal synaptic integrity and ROS levels in relations to neurodegeneration, core AD proteinopathies, and cognitive status. We assessed atrophy, early apoptosis, cell death markers, ROS levels, and pre- and post-synaptic markers by histological and mass spectrometry analyses in post-mortem retinas from confirmed AD dementia and mild cognitive impairment (MCI due to AD) patients, compared to age- and sex-matched subjects with normal cognition (NC). Pearson's (*r*) correlation analyses determined the relationship between retinal synaptic biomarkers and other AD-related retinal parameters, correlating these findings with brain pathology and cognition. : Proteomics analysis in AD patients' retinas revealed a strong link between synaptic loss and neurodegeneration. MCI and AD retinas exhibited highly significant neurodegeneration (Nissl staining) in the outer nuclear layer (ONL; 28%; 23%), inner nuclear layer (INL; 38%; 21%), and ganglion cell layer (GCL; 54%; 52%), accompanied by elevated ROS levels (1.9; 2.2-fold; by DHE staining), respectively, compared to NC controls. Marked pre- (synaptophysin: 56%; 77%) and post- (PSD95: 44%; 66%) synaptic losses were detected in the inner and outer plexiform layers of MCI and AD patients, along with strong negative correlations with the accumulation of retinal pSer396-tau, $A\beta_{42}$, and gliosis markers. AD retinas also exhibited significant increases in apoptotic markers. Remarkably, neurodegeneration and retinal synaptic loss, especially of pre-synaptic markers (VGLUT1, synaptophysin), strongly correlated with the severity of CDR or MMSE cognitive scores (r = 0.75-0.84; $p<0.0001$). Retinal post-synaptic markers (e.g., PSD95) negatively correlated with the Braak stage and ABC score (r = 0.61-0.68; $p<0.001$). Our study reveals pronounced retinal synaptic and neuronal degeneration at sites of pSer396-tau and Aβ42 aggregation, coupled with increased retinal ROS in MCI and AD patients. Elevated retinal oxidative stress may contribute to synaptic loss and neuronal death. These findings suggest that retinal synaptic loss and neurodegeneration could predict AD status.

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Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.21/C130

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

Support: NIH Grant 1R15AG066122-01
University of West Florida Office of Undergraduate Research

Title: Identifying biomarkers using phage-display in Alzheimer's disease

Authors: *R. P. GUTTMANN[1], **M. L. SCOTT**[1], S. M. JONES[2], S. L. TRUAX[1], E. E. SISSKIN[1], C. M. KILPATRICK[1], K. J. WILLIAMSON[1];
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Abstract: The development of biomarker-detection assays using biofluids such as cerebrospinal fluid (CSF) or blood is a critical link in the search for preventing or reversing Alzheimer's disease (AD) for multiple reasons. First, biomarkers are objective measures that can aid in diagnostic accuracy and serve as a means of monitoring disease progression or therapeutic effectiveness. Second, discovering additional biomarkers will provide new insights into the underlying biochemical changes present in AD. The present study aims to build upon the current array of clinically used CSF/blood biomarkers by using phage display to identify additional AD-related post-translational modifications (PTMs) of the tau protein. The present pilot work utilized a landscape phage library of random 7- or 12-mer peptides to identify potential PTMs differentiating AD from control subjects. Briefly, confirmed AD and control subject CSF were incubated on a total-tau antibody ELISA plate. After washing, phage were incubated, followed by additional washing steps to remove unbound phage. To elute the phage, enzymes to targeted PTMs were added. Phage were then collected and amplified, and the process was repeated to enrich the phage pool for the best binding phage. ELISAs were then conducted using individual phage clones to quantify phage binding to AD or control tau. Specifically, we observed differential phage detection of tau PTMs, including SUMOylation, N-linked glycosylation, and ubiquitination between AD and control CSF samples. The overall study aims to validate these observations in additional subjects and identify the modified sites. As a result of these studies, we propose to develop a phage-based array detection method to improve the quality of assessment for those living with or likely to develop AD.

Disclosures: R.P. Guttmann: None. **M.L. Scott:** None. **S.M. Jones:** None. **S.L. Truax:** None. **E.E. Sisskin:** None. **C.M. Kilpatrick:** None. **K.J. Williamson:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.22/C131

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

Support: National Institute on Aging (NIA) grant P30AG066512
National Institute on Aging (NIA) grant P30AG008051

Title: Microstructural Changes of the Temporal Lobe in Early-Stage Alzheimer's Disease

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Abstract: Subjective cognitive decline (SCD) and mild cognitive impairment (MCI) are preclinical and prodromal stages of Alzheimer's Disease (AD). Our previous work has indicated microstructural changes in the hippocampus in individuals with SCD and MCI compared to cognitively normal control participants without subjective complaints (NC). Here, we extend this work by examining microstructural and volumetric changes in the temporal lobe in both SCD and MCI versus NC participants using both diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI).Imaging, behavioral, and cognitive data were obtained from participants aged 52 to 92 years old (36 NC, 105 SCD, and 41 MCI). Diffusion-weighted images were used to derive two DTI metrics, fractional anisotropy (FA) and mean diffusivity (MD), and three NODDI metrics, neurite density index (NDI), orientation dispersion index (ODI), and isotropic volume fraction (ISO) for each subject. Average values of each of these metrics were extracted from 12 bilateral temporal lobe regions. Between-group differences were examined using multiple linear regression models that controlled for age and gender. Group differences were considered significant for p-values < 0.05.The MCI group showed a smaller volume in the right temporal pole region compared to both HC and SCD groups, and in the entorhinal, left middle temporal and right transverse temporal regions compared to the SCD group. In the SCD group, there was a notable decrease in NDI observed in the left transverse temporal, right inferior temporal and right middle temporal regions compared to the HC group, and a decrease in ODI exhibited in right superior temporal and right transverse temporal regions. Furthermore, a significant decrease in FA was observed in the left superior temporal region, and increased MD was noted in both transverse temporal regions, for the MCI group versus the HC group. Notably, marginally significant decreased FA and increased MD were found in the left transverse temporal and left superior temporal regions in the MCI group, respectively (p-values < 0.07). In summary, both volumetric and microstructural differences were observed in the MCI compared with the NC group. The earlier SCD stage showed no detectable volumetric changes, however, microstructural differences suggestive of neurite loss were noted. These results suggest that microstructural changes may precede atrophy in the temporal lobe. These changes could potentially serve as a biomarker for the early detection and prevention of AD.

Disclosures: M. Li: None. **Y. Sui:** None. **A.V. Masurkar:** None. **K. Marsh:** None. **T.M. Wisniewski:** None. **H. Rusinek:** None. **M. Lazar:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.23/C132

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

Support: NRF-2019R1A5A2026045

Title: Atypical centile of intrinsic brain activity pattern in Alzheimer's disease

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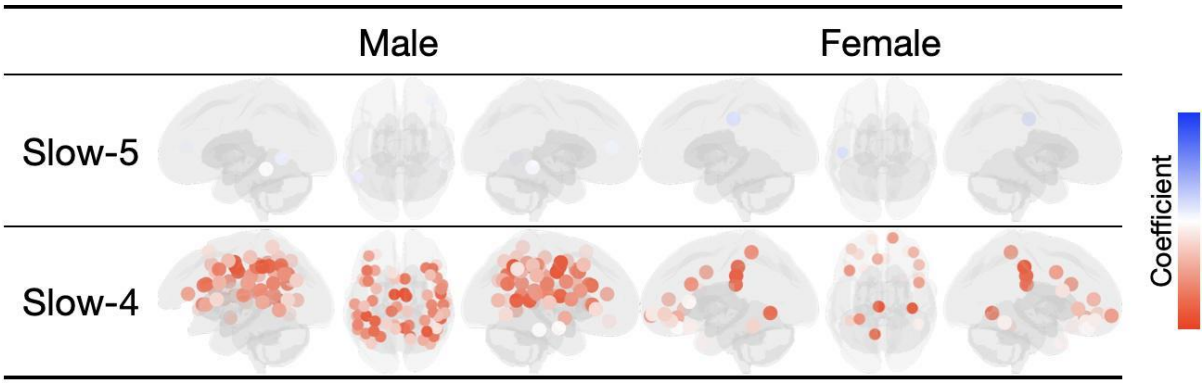
Abstract: The progression of neurodegenerative disease, especially Alzheimer's disease (AD), is not consistently specified. Thus, recent studies efforts to identify developmental trends using neuroimaging are increasing. In addition, normative models can be a useful method to investigate individual heterogeneity in relation to diseases. This study aims to examine the trajectories based on fractional amplitude of low-frequency fluctuation (fALFF) and elucidate intrinsic patterns at different stages of dementia progression.This study is based on 633 subjects (age 70.23 ± 9.42) obtained from Open Access Series of Imaging Studies 3 (OASIS-3). The structural and resting-state functional images were acquired using Siemens 3.0T scanner with 16-channel head coil. All preprocessing procedure is processed using SPM12 in MATLAB. Then, fALFF is calculated as a fraction of the sum of amplitudes within a specific frequency spectrum for each subject. Each region was defined using Schaefer 200 atlas. According to Buzsaki and Draguhn (2004), frequency spectrum is specified by 5 ranges: classic (0.01-0.1), slow-2 (0.01-0.27), slow-3 (0.027-0.73), slow-4 (0.73-0.198), slow-5 (0.198-0.25). Gaussian process regression was conducted to predict normative trends of fALFF and we calculated deviation between predicted and observed value.We found a similar association between frequency spectrum and mini-mental state examination (MMSE) in both male and female. Especially, deviations from low frequency band are positively significant in regions including somatomotor area and temporal area. Furthermore, there were negative associations in slow-5 frequency spectrum range.The frequency bands slow-4 and slow-5 are known to be related to gray matter signals. Since most high-order cognitive functions are executive in the gray matter, deriving significant association between these low frequency spectrums and MMSE. Therefore, higher variability within resting-state functional MRI can be explored across each frequency range, enabling the identification of intrinsic patterns in AD.



Disclosures: D. Yeo: None. **B. Park:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.24/C133

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

Support: National Science Foundation Award No. IIS-2014391

Title: Artificial Intelligence-Enabled Alzheimer's Biomarker from Breathing Signals

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Abstract: For biomarkers detecting Alzheimer's Disease (AD), it's crucial that they can be measured easily and repeatedly. Easy measurements enable early diagnosis and timely treatment, while repeatable measurements facilitate the monitoring of disease progression or remission. Ideally, biomarkers should be measurable at home, allowing those far from medical centers to access testing. However, current AD biomarkers, including brain imaging techniques and cerebrospinal fluid (CSF) analysis, are expensive and can only be conducted in hospital settings. In this study, we present an innovative biomarker for detecting AD using breathing signals during sleep. For the first time, we demonstrate that it's possible to detect AD just from respiration signals. Our biomarker is both easily accessible and repeatable at home, as nocturnal breathing signals can be measured with wearable respiratory effort belts, commonly used in polysomnography. Alternatively, smart radio devices driven by recent advancements in wireless technology can analyze radio signals reflected off a person's body to remotely measure breathing without wearable sensors or body contact (Yue et al., 2018).
We developed our biomarker using a deep learning model that is trained to take nocturnal

breathing signals as input and output the probability of the individual having AD. We evaluated this model on 6,572 individuals from two public sleep study datasets, the Sleep Heart Health Study (SHHS) and the MrOS Sleep Study (MrOS), which include 103 AD patients and 6,469 healthy controls. The evaluation used the area under the receiver operating characteristic curve (AUROC) as the metric. We performed a four-fold cross-validation, randomly splitting the data into four folds, training the model on three folds, and testing on the remaining fold. As a result, our model achieved an AUROC of 0.815 ± 0.009. This result has the potential to improve the early detection of Alzheimer's Disease (AD) by enabling continuous, low-burden home testing for individuals at risk due to family history or genetic factors. The use of our breathing-based biomarker allows those at risk to regularly monitor themselves without requiring expensive or invasive procedures. If flagged by the AI model, these individuals can then be prioritized for further evaluation with more costly imaging techniques, helping healthcare systems efficiently allocate resources and ensure that patients receive timely and accurate diagnosis and treatment.

Disclosures: H. He: None.

Poster

PSTR450: New Biomarkers for Alzheimer’s and Parkinson’s Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.25/C134

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

Support: NRF of Republic of Korea 2018R1D1A3B07047960
Soonchunhyang University Research Fund

Title: Nox4 promotes alzheimer's disease and parkinson's disease by specifically causing mitochondrial dysfunction and ferroptosis in astrocytes.

Authors: *S. YI;
Dept. of Biomed. Lab. Sci., SoonChunHyang Univ., Asan, Korea, Republic of

Abstract: Oxidative stress and mitochondrial dysfunction are well-documented contributors to neurodegenerative diseases, notably Alzheimer's disease (AD) and Parkinson's disease (PD). NADPH oxidase 4 (NOX4), a major producer of reactive oxygen species (ROS), plays a pivotal role in the pathogenesis of these diseases by promoting ferroptosis in astrocytes. Our study reveals that NOX4 levels are significantly elevated in astrocytes from the cerebral cortex of AD patients and APP/PS1 double-transgenic mouse models, as well as in the hippocampus of PD patients and MPTP-induced PD mouse models. These elevated NOX4 levels correlate with increased lipid peroxidation markers such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), indicating enhanced oxidative stress. Furthermore, NOX4 activation disrupts mitochondrial metabolism, evidenced by inhibited mitochondrial respiration and ATP production, and increases mitochondrial fragmentation in human astrocytes. This mitochondrial

dysfunction is associated with the upregulation of neuroinflammatory cytokines myeloperoxidase (MPO) and osteopontin (OPN), further contributing to the oxidative environment conducive to ferroptosis. Our findings suggest that NOX4-induced ferroptosis, via oxidative stress and mitochondrial abnormalities, significantly contributes to astrocyte pathology in AD and PD, highlighting a potential therapeutic target for mitigating disease progression.

Disclosures: S. Yi: None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.26/C135

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

Support: American University in Cairo (Bartlett Fund for Critical Challenges -2021 and Faculty Support Grants-2023
Mansoura University competitive grant (Mu-Med-20-31)

Title: Serum alpha-synuclein and inflammatory markers profile in an Egyptian Alzheimer's and Parkinson's Diseases patients: a pilot study

Authors: *S. A. HEIKAL[1], M. M. SALAMA[2];
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Abstract: Alzheimer's and Parkinson's disease are the most common neurodegenerative diseases. In the current study, we explored the potential of blood-based markers to differentiate Alzheimer's disease (AD) and Parkinson's disease (PD) from healthy controls using ELISA assays via measuring the serum level of α-Syn and panels of inflammatory cytokines in the small pilot cohort of Egyptian volunteers. With the ongoing genetic studies, upcoming data suggest that it is not trivial to revisit the findings reported in specific populations to be tested in each ancestor of different genetic and environmental backgrounds. A total of 42 participants were recruited from the Neurology department, Suhag University Hospital, including 18 AD cases, 9 PD cases, and 15 healthy controls. Clinical and demographic characteristics were well-matched among the three groups. The current data is the first to provide evidence in an Egyptian cohort that aligns with earlier reports that serum level of α-synuclein can be a specific marker for distinguishing PD patients from healthy individuals but not AD patients. Both AD and PD, however, exhibited shared neuroinflammatory profiles with elevated IL-6 and decreased IL-10, hinting at a common inflammatory component despite their distinct etiologies. While trends toward increased IL-1β and TNF-α were observed in AD, the lack of statistical significance suggests a more limited rolein its pathogenesis or the need to expand the sample size. These findings, although promising and the first of a kind to be conducted in Egyptian patients,

necessitate further investigation with larger sample sizes to solidify these markers; potential for diagnosis and fully unravel the specific roles of individual cytokines in each disease.

Disclosures: S.A. Heikal: None. **M.M. Salama:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.27/C136

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

Support: Lilly Research Award Program

Title: Discovery of novel biomarker candidates for peripheral forms of alpha-synuclein and their relation to Lewy body pathology

Authors: *J. HENSEL[1], K. RUSS[2], B. MA[3], D. DRIVER[3], J. DAGE[1];
[1]Neurol., Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Med. and Mol. Genet., Indiana Univ. Sch. of Med., Indianapolis, IN; [3]BioTDR, Eli Lilly, San Diego, CA

Abstract: Alpha-synuclein (aSyn) is pre-synaptic protein abundant throughout the central nervous system. Aggregation of aSyn into intraneuronal protein aggregates, called Lewy bodies, is the hallmark pathological feature of neurodegenerative disorders called synucleinopathies, which include Parkinson's disease (PD) and dementia with Lewy bodies (DLB). The current gold standard for antemortem diagnosis of Lewy pathology is the cerebrospinal fluid (CSF) real-time quaking-induced conversion (RT-QuIC) assay. However, to date, this approach has had limited success in blood due to lack of selectivity against the peripheral forms of aSyn or lack of sensitivity for forms specific to Lewy bodies. The aim of this study is to discover blood-biomarkers specific for Lewy body diseases (LBD) using immunoprecipitation (IP) followed by mass spectrometry (MS) and synuclein seed amplification (SSA) assays. We prepared 14 in house aSyn antibodies with 12 targeting amino acids in the C-terminus, one targeting amino acids in the N-terminus, and one targeting the pathological modification of phosphorylation at Serine 129 (pS129). Our results show out of the 13 in house aSyn antibodies, we observe a differential binding phenotype in IP followed by Western blot with seven antibodies preferring high molecular weight (HMW) aSyn species, three preferring the monomeric aSyn species, and three having almost equal preference for HMW and monomeric aSyn species. From this, we isolated the top two LBD antibody biomarker candidates in each category for further analysis. We aim to further rank these candidates by their binding affinity using biolayer interferometry and antigen down enzyme-linked immunosorbent assays (ELISA). After selecting the top LBD antibody biomarker candidates, we will perform IP using human plasma from either healthy control (HC) or Alzheimer's disease (AD) subjects with matched CSF aSyn RT-QuIC data. This IP product will be analyzed by MS and RT-QuIC followed by an *in vitro* cell culture seed

propagation assay. This will differentiate between true HC, AD, and AD patients with LB co-pathology thereby highlighting the antibody specificity Lewy pathology. Furthermore, we will analyze human plasma samples from a separate cohort of HC, PD, and AD subjects utilizing the same LBD biomarker candidates to determine the biomarkers' ability to distinguish between HC, AD, and LBD diagnosis, confirmed by CSF aSyn RT-QuIC. The discovery of blood-biomarkers for Lewy pathology will aid in diagnosis and clinical trial enrollment as well as therapeutic monitoring when disease modifying treatments are advanced into the clinic.

Disclosures: J. Hensel: A. Employment/Salary (full or part-time):; Indiana University School of Medicine. **K. Russ:** A. Employment/Salary (full or part-time):; Indiana University School of Medicine. **B. Ma:** A. Employment/Salary (full or part-time):; Eli Lilly and Co. **D. Driver:** A. Employment/Salary (full or part-time):; Eli Lilly and Co. **J. Dage:** A. Employment/Salary (full or part-time):; Indiana University School of Medicine.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.28/C137

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

Support: Parkinson's Foundation Visiting Scholar Award

Title: Medial temporal lobe atrophy and category fluency performance in Parkinson's disease amnestic mild cognitive impairment

Authors: *D. POURZINAL[1], A. BAKKER[2], G. PONTONE[3], N. DISSANAYAKA[1];
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Abstract: Background: Memory-dominant (amnestic) Mild Cognitive Impairment (aMCI) is associated with increased dementia risk in Parkinson's Disease (PD). Some PD-aMCI participants are also impaired in category fluency, a measure of semantic memory and the most consistent neuropsychological predictor of cognitive decline in PD. As the medial temporal lobe (MTL) plays a critical role in memory processes, this study aimed to evaluate the relationship between structural integrity of MTL subfields and category fluency in PD-aMCI to propose possible biomarkers of dementia risk in PD. **Method**: 43 participants (14 PD-aMCI, 19 PD with normal cognition (PD-NC) and 20 healthy controls (HC)) underwent structural Magnetic Resonance Imaging (MRI; Siemens 3T Scanner) and comprehensive cognitive assessment. Bilateral hippocampus, entorhinal cortex (ERC), parahippocampal cortex, and perirhinal cortex (Brodmann area (BA) 35 and 36) volumes were extracted using the Automated Segmentation of Hippocampal Subfields (ASHS) software and compared across groups using Kruskal-Wallis/Wilcoxon tests. Spearman's rho correlations were performed between MTL volumes and

Delis-Kaplan Executive Function System (D-KEFS) category fluency (animals / boys' names). All analyses were controlled for age, sex, and intra-cranial volume. **Results**: PD-aMCI exhibited reduced bilateral posterior hippocampi ($p < .0016$) and bilateral BA35 ($p < .0013$) volume compared to HC. These areas were also reduced in PD-aMCI compared to PD-NC, although these analyses did not survive multiple comparison adjustment. HC showed increased bilateral BA36 volume compared to PD-aMCI (p<.0013) and right BA36 volume compared to PD-NC ($p = .0008$). In PD-aMCI, the left ERC ($r_s = .84$, $p = .0024$) and right BA35 ($r_s = .86$, $p = .0013$) were positively correlated with category fluency. **Discussion**: Our findings establish the role of MTL atrophy in PD-aMCI and directly relate the structural integrity of this region to category fluency performance. These results highlight sensitivity of the category fluency task to structural alterations in PD as well as the potential utility of MTL structural integrity as a biomarker for dementia risk in PD.

Disclosures: D. Pourzinal: None. **A. Bakker:** None. **G. Pontone:** None. **N. Dissanayaka:** None.

Poster

PSTR450: New Biomarkers for Alzheimer's and Parkinson's Diseases and Other Neurodegenerative Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR450.29/C138

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

Title: Longitudinal study of biomarkers in a goat model of neurodegeneration

Authors: *A. S. OYADEYI[1], R. ADAM[2], N. ACKERMANS[3];
[1]Dept. of Biol. Sci., Univ. of Alabama, Tuscaloosa, AL; [2]Biol. Sci., The Univ. of Alabama, Tuscaloosa, AL; [3]Univ. of Alabama, Tuscaloosa, AL

Abstract: Traumatic brain injury (TBI) affects 69 million individuals worldwide each year, and 190 Americans die daily from TBI-related injuries. From the first impact to the head, pathological progression is complex, and therefore difficult to diagnose and treat. Rodent models have not yielded translatable biomarkers for TBI diagnosis because of neuroanatomical and lifespan differences compared to humans. Studies from our group on wild muskoxen and bighorn sheep have shown signs of TBI and chronic traumatic encephalopathy (CTE). We thus hypothesize that a large animal model with natural headbutting behavior would sustain cumulative brain injuries measurable by fluid biomarkers. We propose goats as a translational research model for studying post-TBI neurodegeneration. Continuous video recording of headbutting behavior in three male domestic goats (*Capra hircus*) was paired with a head-mounted accelerometer to record head impact force. Positron emission tomography (PET) - MRI of the brains was performed, and cerebrospinal fluid, blood, and saliva were sampled monthly for six months. Multiplex assay, immunoblotting, and immunohistochemical methods were applied to prefrontal cortex tissue to quantify markers of neuropathology used to diagnose

Alzheimer's disease and CTE in humans. Markers included amyloid precursor protein, amyloid beta, phosphorylated and total tau, glial fibrillary acidic protein, neurofilament L, and S100B. Neurodegeneration in this model would show elevated fluid biomarker protein levels combined with qualitative neuropathological patterns. The presence of aberrant proteins, gliosis, and cytoskeletal damage are consistent with long-term neurodegeneration. Overall, data from this large animal model using natural headbutting behavior would enable the study of neurodegeneration more longitudinally without the artefacts of experimental TBI induction. A large animal model more comparable to humans can provide insight into the onset of the neuropathological processes of post-TBI dementia in humans.

Disclosures: A.S. Oyadeyi: None. **R. Adam:** None. **N. Ackermans:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.01/C139

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS P50NS123103

Title: Electrophysiologic mechanisms of movement initiation and response inhibition in Parkinson's disease

Authors: *V. DUONG[1], S. BORGHEAI[2], R. JAFARI DELIGANI[2], E. OPRI[3], F. ISBAINE[2], N. AU YONG[2], S. MIOCINOVIC[2];
[1]Biomed. Engin., Georgia Tech/ Emory Univ., Atlanta, GA; [2]Emory Univ., Atlanta, GA; [3]BME, Univ. of Michigan, Ann Arbor, MI

Abstract: Motor control disruptions and their electrophysiologic mechanisms are yet to be understood in Parkinson's disease (PD). Specifically, much is still unknown about the circuits responsible for proactive inhibition and how they were affected by PD. Proactive inhibition refers to preparatory mechanisms that facilitate action inhibition (i.e., enables a person to act with restraint). We investigate this problem by studying electrophysiological activity in the sensorimotor cortex, inferior frontal gyrus (IFG) and the subthalamic nucleus (STN). We hypothesized that IFG and STN modulate activity when proactive inhibition is engaged, while sensorimotor cortex responds during movement initiation and execution. Utilizing intracranial recordings, we analyzed data from 17 PD patients (mean age: 59.5 ± 8.1; 13M, 4F; mean MDS-UPDRS III off-levodopa: 42.3 ± 12.2) undergoing awake deep brain stimulation (DBS) surgery when they were engaging in GoNoGo (GNG) task. Our recordings included subdural electrocorticography (ECoG) over sensorimotor and prefrontal cortex and local field potential (LFP) in the STN using DBS electrodes. Patients performed 120 trials of GNG task and 45 trials of GoOnly (GO) task (a control task where a response was always expected). Our preliminary ECoG signals were segmented and averaged to generate event-related potentials (ERP) for the

cue and go signals and hand-button response of both tasks. The median reaction time was 363 ± 124 ms during GO task compared to 451 ± 107 ms during GNG task which was significantly different (*p = 0.0075, Wilcoxon's paired sign-rank test*). The response time for GO and GNG significantly correlated with motor disease severity measured by MDS-UPDRS III score (*p = 0.008, R2=0.4 and p = 0.025, R2=0.31, respectively*), while the rate of commission errors (responding on NoGo signal) did not. The ERP was present over the primary motor cortex during action execution in 6 patients (out of 12 who had ECoG). The ERP started on average, 385 ± 155 ms and 277 ± 148 ms before the button press for the GO and GNG task, respectively (*p = 0.03, Wilcoxon's paired sign-rank test*). The ERP was more pronounced when using the hand contralateral to the recorded hemisphere in all patients. There was no correlation between ERP onset time and PD severity, GO and GNG reaction time. There was no ERP over the premotor cortex during motor planning and initiation phase of the task. In conclusion, our early findings indicate that response times are related to motor disease severity. We also showed that motor ERP are larger over the cortical area contralateral to movement and the presence of inhibition delays the ERP onset time.

Disclosures: V. Duong: None. **S. Borgheai:** None. **R. Jafari Deligani:** None. **E. Opri:** None. **F. Isbaine:** None. **N. Au Yong:** None. **S. Miocinovic:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

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Program #/Poster #: PSTR451.02/C140

Topic: C.03. Parkinson's Disease

Support: Changping Laboratory
China Postdoctoral Science Foundation 2022M720529
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National Natural Science Foundation of China 82090034
National Key R&D Program of China 2017YFE0103600
Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health of Anhui Province 2020xkjT05

Title: The role of the somato-cognitive action network in Parkinson's disease

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Abstract: Functional disruptions in Parkinson's disease (PD) correspond with complex, nonspecific motor symptoms, including bradykinesia, tremor, rigidity, and posture and gait dysfunction. The newly-recognized somato-cognitive action network (SCAN), located in M1, is posited to be important in movement coordination, action planning, and axial body movement. Its strong connectivity with cortical and subcortical networks responsible for movement and action planning puts it in an ideal position to coordinate these functions. In the present study, we investigated the role of the SCAN in PD pathophysiology, using precision functional mapping. We analyzed functional MRI data from hundreds of individuals across 6 independent datasets. We estimated the functional connectivity (FC) between subcortical regions implicated in PD and the cortical motor networks (SCAN, M1 effector regions), in both PD (n=166) and healthy controls (n=60). Compared to healthy controls, the PD group exhibited significantly greater SCAN FC with most subcortical regions (subthalamic nucleus, substantia nigra, external globus pallidus, putamen; independent samples t-tests, all p's < 0.001, FDR-corrected), consistent with the abnormal subcortico-motor cortex hyperconnectivity described in the PD literature. In the PD group, the subcortical FC with the SCAN was higher than with the effector-specific regions of M1 (paired samples t-tests, all p's < 0.001, FDR-corrected), indicating that the SCAN is a more integral part of PD circuitry. We also investigated SCAN FC with various deep-brain stimulation (DBS) targets employed in the treatment of PD, using a collection of datasets (N = 275). The stimulation sweet spot for each target was consistently more highly connected to the SCAN than to effector-specific regions (paired samples t-tests, all p's < 0.001, FDR-corrected). Finally, to reveal a direct causal link between the SCAN and PD, we performed a 14-day transcranial magnetic stimulation intervention in 38 patients with PD, where 18 patients received SCAN stimulation and 20 M1 effector stimulation. While both groups experienced an alleviation in symptoms, the SCAN group exhibited greater improvements following treatment (independent samples t-test, $p < 0.05$). In sum, the SCAN appears to play a pivotal role in PD, as it exhibits substantial functional abnormalities, is selectively involved in neuromodulatory therapies, and demonstrates causal links with clinical improvement. The SCAN is a testable candidate neuromodulatory target for PD treatment and warrants evaluation in future clinical trials.

Disclosures: J. Ren: None. **W. Zhang:** None. **L. Dahmani:** None. **Q. Hu:** None. **C. Jiang:** None. **Y. Bai:** None. **G. Ji:** None. **Y. Zhou:** None. **P. Zhang:** None. **W. Wang:** None. **K. Wang:** None. **M. Wang:** None. **L. Li:** None. **D. Wang:** None. **H. Liu:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.03/C141

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's [ASAP-020572]

Title: Computer simulation of excitability changes in primary motor cortex pyramidal tract neurons In mouse-model parkinsonism

Authors: *D. DOHERTY[1], A. J. H. NEWTON[2], L. CHEN[3], H.-Y. CHU[4], W. W. LYTTON[5]; [1]SUNY Downstate Hlth. Sci. Univ., Pittsburgh, PA; [2]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [3]Neurodegenerative disorder Dept., Van Andel Res. Inst., Grand Rapids, MI; [4]Van Andel Inst., Washington DC, MI; [5]Physiology/Pharmacology, SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

Abstract: Recent evidence suggests that the primary motor cortex (M1) layer 5B pyramidal tract (PT5B) neurons show a decreased intrinsic excitability in mouse models of parkinsonism, which perhaps plays an important role in the pathophysiology of parkinsonian motor symptoms. PT5B neurons project to outputs in the brainstem and the spinal cord, leading to the direct motor expression of PD pathology. We used a multicompartment computational model of PT5B to capture changes in ion channel densities that may cause the decreased intrinsic excitability in parkinsonian electrophysiology and then we investigated the activity patterns of the M1 network with these PT5B changes. We used NEURON with BluePyOpt to fit electrophysiological data from 39 PT5B cells from healthy controls and 30 from 6-OHDA-treated PD mice. Optimization was based on 16 features extracted from current-clamp recordings; five passive measures, eight firing measures, and three spike-shape features. Model parameters included passive membrane properties, ion channel conductances, and calcium buffering. This provided a good fit for all but three cells. Using NEURON/NetPyNE simulators, we placed these PT5B cells in an in vivo M1 network simulation, driven by ascending input from the thalamus and from other cortical areas. Simulated 6-OHDA-treated mouse PT5B neurons in an otherwise unmodified simulated M1 network resulted in major changes in LFP oscillatory power in the parkinsonian state: an order of magnitude increase in beta band power around 15 Hz in the rest state, and a lesser increase in beta power in the parkinsonian activated (movement) state. We demonstrated that relatively small changes in PT5B neuron excitability altered the patterns of activity throughout the M1 circuit. In particular, the decreased PT5B neuron excitability resulted in increased beta band power, which is a signature of PD pathophysiology.

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Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.04/C142

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant R01NS123424-01
NIH Grant T32 GM008804

Title: Introducing variability into the inter-pulse interval of electrical brain stimulation in the MFB and mPFC alters dopaminergic release

Authors: *A. HAMILTON[1], A. VISHWANATH[2], N. WEINTRAUB[1], S. L. COWEN[3], M. L. HEIEN[1];
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Abstract: Striatal dopaminergic release plays a role in decision making and reward-guided learning. Electrical brain stimulation has been used to investigate the neural circuitry involved in reinforcement-driven behaviors, and high-frequency deep-brain stimulation is an established treatment for Parkinson's disease. These forms of electrical brain stimulation use stimulation patterns with fixed frequencies or fixed inter-pulse intervals. However, previous studies show that neural circuits are more responsive to variable inter-pulse intervals. In this study, we investigate how variable inter-pulse interval stimulation patterns affect downstream dopaminergic release in the nucleus accumbens (NAc). The stimulation targeted the medial forebrain bundle (MFB) and the medial prefrontal cortex (mPFC), two regions with strong projections to the NAc and the ventral tegmental area (VTA). Stimulating the MFB directly activates dopaminergic axons and evokes downstream dopamine release. Conversely, stimulating the mPFC activates a multi-synaptic circuit through glutamatergic projections to the VTA and NAc. **Methods:** A carbon-fiber microelectrode was implanted in the NAc to detect dopamine by fast-scan cyclic voltammetry (FSCV) in anesthetized, male, Sprague-Dawley rats (310-400 g, n = 5 each stimulation region). A bipolar stimulating electrode was lowered into either the MFB or mPFC. Stimulation patterns lasted 10 seconds and were generated with differing degrees of inter-pulse variability and constrained to have an average frequency of 10 Hz or 20 Hz. Local variance was used to quantify the variability of the inter-pulse interval. *In vivo* dopaminergic release was compared to modeling simulations predicting the dopamine release of these variable stimulation patterns. **Results:** Higher frequencies of stimulation in the MFB caused significantly more dopamine release while there was no significant change in dopamine release when stimulating the mPFC. Similarly, the MFB is more responsive to changes in frequency as indicated by the tight correlation of the stimulation pattern frequency and the subsequent dopamine release. To isolate the effects of local variance from frequency, stimulation patterns were generated with a repeating, four-pulse unit with specific local variance values. In this case, increased variability of the inter-pulse interval evoked less release during both MFB and mPFC stimulation. These results are confirmed with computational modeling of dopaminergic release. These results indicate that MFB stimulation is driven more by instantaneous frequency.

Disclosures: A. Hamilton: None. **A. Vishwanath:** None. **N. Weintraub:** None. **S.L. Cowen:** None. **M.L. Heien:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.05/C143

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's (ASAP) 020519

Title: Changes in the macro-architecture of basal ganglia loops with the primary motor cortex of the parkinsonian macaque

Authors: *A. C. BOSTAN[1], D. KASE[1], M. R. HAKIM[2], M. K. FRUM[1], W. R. STAUFFER[1], R. S. TURNER[1], P. L. STRICK[1];
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Abstract: The basal ganglia participate in two distinct networks with the motor cortex. The primary motor cortex (M1) sends inputs to dorsal portions of the putamen (PUTd). The PUTd sends a multi-synaptic output back to M1 to form a "closed-loop circuit" (CLC). Transneuronal tracing using rabies virus in nonhuman primates indicates that ventral regions of the putamen (PUTv) also have a multi-synaptic output to M1. However, the PUTv is not a target of inputs from M1. Instead, PUTv receives projections from limbic regions of the cerebral cortex and the amygdala. Thus, the PUTv forms an "open-loop circuit" (OLC) with M1. The OLC may provide a pathway for emotional functions to affect motor control. Motor signs of Parkinson's disease (PD) are associated with dopaminergic depletion of PUTd and resulting dysfunction of the CLC. Dopaminergic innervation of the PUTv is relatively spared in the parkinsonian state. Here, we investigated the integrity of CLC and OLC in the parkinsonian state. We injected rabies virus (RV) into the arm region of M1 in normal macaques and macaques rendered parkinsonian through the administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). We set the survival time to allow for retrograde transneuronal transport of RV from M1 to third-order medium spiny neurons (MSNs) in the PUT. We observed robust transport of RV through the OLC to MSNs in the PUTv of normal and MPTP-treated macaques. However, RV transport to the dopamine-depleted PUTd of MPTP-treated macaques was drastically reduced. Previous studies provided evidence that dopamine depletion results in a reduction of spines and increased excitability of MSNs in the PUT, but have reported no cell loss. Our results indicate that dopamine depletion in the PUTd may impair synaptic output from MSNs, which could result in dysregulation of the CLC and the manifestations of PD. On the other hand, our results revealed that the OLC from the PUTv to M1 remains intact in the parkinsonian state. Preserved OLC function may help to explain the remarkable motor abilities that PD patients can exhibit in the presence of strong emotional stimuli (paradoxical kinesia). Further, our results suggest that the OLC may be a new therapeutic target for the restoration of function in the parkinsonian state.

Disclosures: A.C. Bostan: None. **D. Kase:** None. **M.R. Hakim:** None. **M.K. Frum:** None. **W.R. Stauffer:** None. **R.S. Turner:** None. **P.L. Strick:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

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Program #/Poster #: PSTR451.06/C144

Topic: C.03. Parkinson's Disease

Support: NIH Grant 5R01NS117547-05

Title: Correlations between local neural activity derived using resting state functional MRI measures and clinical measures in individuals with Parkinson's disease experiencing freezing of gait.

Authors: *T. R. DAVIS[1], V. R. MISHRA[2];
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Abstract: Freezing of gait (FOG) is where those affected are unable to begin walking, turn, or move around in tight spaces. Anywhere from 20-80% of those with Parkinson's Disease (PD), a debilitating disorder characterized by motor dysfunction and cognitive impairment, suffer from FOG and this incidence increases with disease length and severity. Little is known about why FOG occurs, although one theory behind it is because of an alteration in neural connectivity between certain areas of the brain. Neural activity causes low-frequency fluctuations of brain activity which can be measured by amplitude of low-frequency fluctuations (ALFF) and its standardized counterpart, fractional ALFF (fALFF) along with differences in the synchronization of this activity, as measured by Kendall's Coefficient Concordance Regional Homogeneity (KCC-ReHo). Whether or not these differences in regional activity and signal homogeneity are correlated with scores for clinical variables, neuropsychological tests, or physical therapy exam scores is unknown. 15 patients with PD-FOG, 15 with PD-nFOG, and 15 healthy controls (HC) were recruited for this study. All subjects underwent rs-fMRI scans on a 3T Siemens Skyra scanner while in the L-DOPA "ON" state. The rs-fMRI involved gradient-echo T2*-weighted echo-planar imaging (EPI) acquisition (repetition time [TR] = 700 ms, echo time [TE] = 28.4 ms, flip angle = 42°, resolution = 2.3 × 2.3 × 2.3 mm3, 64 axial slices, multiband = 8). All blood-oxygen level dependent (BOLD) data underwent preprocessing using fMRIB Software Library (FSL) and Advanced Normalization Tools (ANTs). Once the BOLD data was preprocessed, ALFF, fALFF, and KCC-ReHo were calculated using RESTplus software and statistical analysis was done using in-house MATLAB scripts with FSL's PALM. We obtained general demographics for all subjects and the disease duration, FOGQ score, levodopa equivalent doses (LEDD), physical therapy tests, and MDS-UPDRS-III scores for each patient with PD. We collected neuropsychological tests scores for all participants. We found a significant correlation between zALFF values for our PD-FOG participants and scores for neuropsychological assessments testing working memory and attention (Weschler Adult Intelligence Scale-Fourth Edition [WAIS-IV] Digit Span Forward subtest). We also found correlations among differences in zALFF values between HC, PD-FOG, and PD-nFOG and test scores assessing attention and working memory. We found no significant correlations between zfALFF or zKCC-ReHo values and the clinical variables, neuropsychological tests, and physical therapy scores of any group.

Disclosures: T.R. Davis: None. **V.R. Mishra:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.07/C145

Topic: C.03. Parkinson's Disease

Title: Assessing changes in whole-brain structural connectivity associated with early-stage Parkinson's Disease using diffusion imaging and tractography.

Authors: *M. MOSHCHIN[1], M. HAEBIG[1], S. HURLEY[2], J.-P. J. YU[3], C. GALLAGHER[1], A. J. SUMINSKI[4];
[1]UW-Madison, Madison, WI; [2]Radiology, Univ. of Wisconsin-Madison, Madison, WI; [3]Univ. of Wisconsin Sch. of Med. and Pub, Madison, WI; [4]Dept. of Neurolog. Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Parkinson's disease (PD) is characterized by the degeneration of neurons in the substantia nigra pars compacta (SNc) that leads to striatal dopamine deficiency. In humans, degeneration of SNc neurons triggers motor symptoms, including bradykinesia, resting tremor, rigidity, and freezing of gait. However, less specific symptoms, such as sleep abnormalities, autonomic nervous system dysfunction, and cognitive changes, may precede motor signs and fulfill the criteria for prodromal PD. Although the onset of motor signs is related to Lewy body accumulation and death of dopaminergic neurons in the SNc, current evidence suggests that more widespread cell loss may account for prodromal and non-motor symptoms of the disease. This pilot work aims to use correlational tractography based on diffusion magnetic resonance imaging (dMRI) to detect in vivo microstructural changes in whole brain networks associated with mild PD and to assess the correlation between these brain-wide changes and PD symptoms. Sixteen (16) participants were recruited through the William S. Middleton V.A. Hospital, University of Wisconsin-Madison clinics as part of this pilot study. Thirteen (13) participants met clinical and imaging criteria for analysis: 8 with mild PD (2 women; mean age, 55.5 ± 2.86; Unified Parkinson's Disease Rating Scale [UPDRS-III] score, 15.68 ± 1.09; Patient Health Questionnaire [PHQ9], 3.88 ± 1.08) and 5 controls (2 women; mean age, 70.4 ± 3.09; UPDRS-III score, 2.6 ± 1.13; PHQ9, 1.2 ± 0.73). Correlational tractography was used to compare whole brain white matter integrity between PD and control groups using DSI-Studio. Correlational tractography found fiber tracks throughout the brain both positively and negatively correlated with disease status (FDR < 0.05, PD vs. Control). Further, quantitative anisotropy (QA) within positively correlated fibers demonstrated a significant linear relationship (i.e. slope) with PHQ9, a measure of depression (T_{11}=2.26, p <0.045). In contrast, QA within negatively correlated fibers demonstrated a significant correlation with UPDRS-III (T_{11}=-2.7, p <0.022) a measure of motor symptom severity. Thus, our pilot work shows differences in the structural characteristics of whole brain networks in early-stage PD. While differences in the diffusion characteristics of cerebral white matter have previously been demonstrated in PD, this has not been done using QA. Further, the correlation between QA and mood or motor function within these Parkinson's relevant networks suggests that QA may provide a powerful new biomarker that should be replicated in larger studies.

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Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.08/C146

Topic: C.03. Parkinson's Disease

Support: NINDS 1P50NS123103
NINDS 1 R01 NS111470
NIH P51-OD011132

Title: Linking progressive forelimb movement impairments to cortical projection neuron activity in the MitoPark mouse model of Parkinson's disease

Authors: *A. PALA[1], Z. XIE[1], E. C. LAPEZA[1], I. MARTINEZ[1], R. MUMED[1], A. GALVAN[1,2], D. JAEGER[1];
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Abstract: Changes in the pattern of neural activity in the basal ganglia and thalamus have been linked to the progression of Parkinson's disease and to the appearance of motor symptoms, especially akinesia and bradykinesia. Much less is known about the contribution of cortical motor circuits, and of cortical projection neurons in particular, to the appearance and progression of parkinsonian motor symptoms. Here, we longitudinally imaged the activity of two mostly non-overlapping populations of layer 5 cortical projection neurons, corticospinal (CSP) neurons and subthalamic nucleus-projecting (STNP) neurons using JEDI-1P, a genetically-encoded voltage indicator (GEVI) in MitoPark mice performing a bilateral forelimb-mediated water-reaching task. A circular cranial window centered on the brain midline enabled us to simultaneously measure the activity of either CSP or STNP neurons of the forelimb regions of primary sensorimotor cortex (S1/M1) and secondary motor cortex (M2) across both cerebral hemispheres over the course of several months. In preliminary behavioral analyses, we found that MitoPark mice showed initial reaching performance and reaction times comparable to that of control littermates, but their reaction times gradually slowed down and their reaching performance progressively decayed. Systemic delivery of L-DOPA/benserazide partially restored reaching performance in MitoPark animals while marginally affecting that of control littermates. The changes in reaching behavior observed in MitoPark mice were accompanied by a reduction in locomotor activity and a decrease in overall coordination and balance as assessed in open field and rotarod assays. In a preliminary analysis of voltage activity of STNP neurons during water-reaching, we found a lateralized increase in S1/M1 activity surrounding the time of contact of the forelimb with the waterspout in both MitoPark and control mice. Ongoing analyses of the spatiotemporal structure of unilateral and bilateral STNP and CSP neuronal activity as reaching performance gradually decays will reveal whether there is a contribution of the STNP-mediated hyperdirect pathway and of direct corticospinal projections to the development of akinetic and bradykinetic motor symptoms in Parkinson's disease.

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Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.09/C147

Topic: C.03. Parkinson's Disease

Title: Modeling the exploratory dynamics of the Indirect Pathway in the Basal Ganglia using a network ofChaotic Attractors

Authors: *S. S. NAIR[1], P. CHARITHA[1], J. SHARMA[3], N. ROHAN[1], S. V. CHAKRAVARTHY[2];
[1]Biotech., [2]Dept. of Biotech., Indian Inst. of Technol. Madras, CHENNAI, India; [3]Electrical and Electronics, Manipal Inst. of Technol., Manipal, India

Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder, caused by the loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNc). We had earlier proposed that when the BG is described using Reinforcement Learning (RL), the Direct Pathway subserves exploitation, while the Indirect Pathway subserves exploration. The putative role of the Subthalamic Nucleus (STN) in exploration, is supported by the loss of complex dynamics in STN under PD conditions. We describe a model of the Basal Ganglia (BG) in which loss of complex dynamics in STN, which is modeled by a network of chaotic Rossler systems, is manifested as impaired performance in Iowa Gambling Task (IGT). The dynamics of the Rossler network are characterised by the parameter 'a', which allows the network to move from a periodic to a chaotic regime, characterised by uncorrelated desynchronised oscillations. The network is tuned to exhibit chaotic behaviour in normal conditions and synchronised periodic oscillations in PD conditions. The network receives feedback via mean-field diffusion from SNc, which controls the collective behaviour of the network. This network also receives inputs (Iext) from the striatum (D2R neurons), which can induce STN transition into a periodic regime. The BG circuitry is trained for IGT using RL. Temporal difference error (δ) is analogous to dopamine in SNc. We define epsilon (ε) as the exploratory parameter, which is a function of δ and linearly controls 'a' in STN. The initial stages of training demand a greater exploration (high ε), which necessitates the network to operate in a chaotic regime. To simulate the dopamine loss in PD condition, the δ value is delimited which in turn constrains ε, restricting STN to a periodic regime. This limits the BG circuit's ability to learn the IGT task. IGT is evaluated by a score computed as the difference between advantageous deck choices and disadvantageous deck choices. The entire task is split into 5 bins, each of 20 picks. Fig. 1 (d) shows that the proposed BG circuit is able to improve the IGT score in normal condition as opposed to in PD condition.

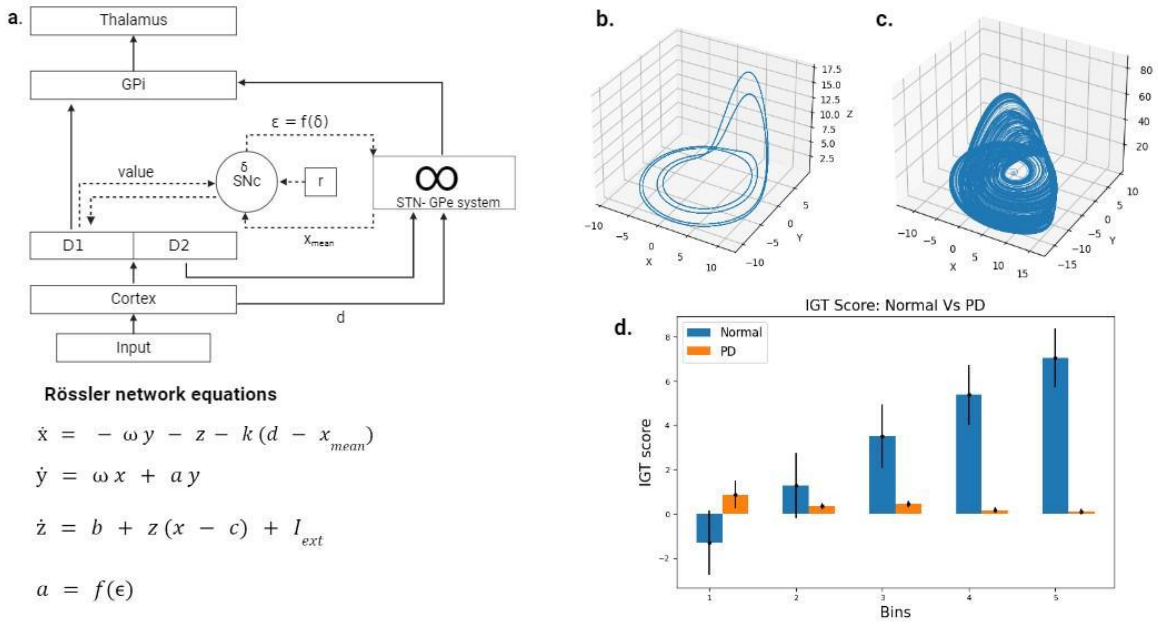

Fig 1. (a) Proposed schematic of Basal ganglia circuitry. (b) Output of Rössler attractor in periodic regime (c) Output of Rössler attractor in chaotic regime. (d) Performance in the IGT

Disclosures: S.S. Nair: None. **P. Charitha:** None. **J. Sharma:** None. **N. Rohan:** None. **S.V. Chakravarthy:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.10/C148

Topic: C.03. Parkinson's Disease

Title: Motor control mechanism similarities of toe tapping and circle drawing in persons with Parkinson's disease

Authors: *R. A. SMITH[1], E. L. STEGEMOLLER[2];
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Abstract: Individuals with Parkinson's disease (PD) demonstrate increased motor variability during continuous movements because these movements involve basal ganglia networks impaired by the disease (Stegemöller et al., 2009). Repetitive finger movements tend to be under discrete control at rates below 2 Hz and continuous control above 2 Hz (Zelaznik et al., 2002). This trend has not been verified for all repetitive movements. The purpose of this study was to examine the relationship between the variability of discrete and continuous movements during circle drawing and toe tapping in participants with PD. It is hypothesized that variability will be

higher during continuous movements and that the change in variability from discrete to continuous movement will be similar between circle drawing and toe tapping. Ten participants with PD completed repetitive toe tapping and circle drawing tasks at two different cueing rates using their more affected side in the on-medication state. Participants drew 1 cm-diameter circles with pacing tones at intervals of 1.25 Hz and 2.5 Hz. They also tapped their toe with pacing tones at intervals of 1.17 Hz and 2.33 Hz. The position of the tip of the pen and toe, respectively, were recorded at 200 Hz using an electromagnetic tracking system. Coefficients of variation (CV) of inter-movement interval (IMI) and circle width or tap amplitude were computed for each pacing condition. The differences in spatial and temporal CV between the pacing conditions were calculated for each task and the correlation between change in CV was used to determine the relationship between tasks. Toe tap IMI CV was significantly greater in the faster pacing condition (.123) than the slower pacing condition (.106, p=.05), suggesting that persons with PD may control toe tapping above 2 Hz using continuous control involving affected basal ganglia networks. Computations of circle drawing IMI CV and correlations in IMI differences are ongoing. Toe tap amplitude was less variable in the fast condition (fast CV=.092, slow CV=.117, $p < 0.01$). Circle width CV was not significantly different between pacing conditions (fast CV =.054, slow CV=.023, p=.51). Differences in spatial CV across affecters are strongly positively correlated (R=.79), suggesting that the mechanism for controlling the spatial parameters of circle drawing and toe tapping at different rates are similar in persons with PD.

Disclosures: R.A. Smith: None. **E.L. Stegemoller:** None.

Poster

PSTR451: Neurophysiology in Parkinson's Disease

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR451.11/C149

Topic: C.03. Parkinson's Disease

Support: RS-2023-00266872

Title: Advancing drug screening platform for Parkinson's disease: A novel in-vitro motor signal system using patient-derived organ-on-a-chip technology

Authors: D. YOU, E. YANG, Y. LEE, H. PARK, K.-J. YOON, D. KIM, ***M. L. CHOI**; KAIST, Daejeon, Korea, Republic of

Abstract: Parkinson's Disease (PD) affects approximately 12 million people globally and manifests as both motor and cognitive impairments due to the degeneration of dopaminergic neurons. The progressive nature of PD underscores a substantial challenge in drug development, notably for middle and late-stage patients. Traditional pharmacological models often fail to replicate the complex aetiology of PD, contributing to high unsuccessful rates in clinical trials. Here, we propose a novel in vitro model that utilizes patient-derived induced pluripotent stem cells (iPSCs) to mimic the neuroanatomical and functional complexities of PD more

accurately.Our approach utilizes iPSCs differentiated into midbrain dopaminergic neurons and GABAergic neurons or each organoid, organized via a microfluidics system to establish a functional inhibitory circuit between the midbrain and cortex. This system not only facilitates a more precise understanding of PD pathophysiology but also provides a robust platform for the evaluation of new therapeutics. The significance of our model lies in its ability to replicate the 'rebound firing theory', where an increase in excitatory motor signals rather than a decrease underpins the motor symptoms of PD. Initial observations indicate abnormal excitatory signals in the thalamus and cerebral cortex of PD patients, which are not present in healthy individuals. By closely mimicking human physiological conditions, our model aims to address the critical failures in PD drug development and provide a pathway for the discovery of comprehensive treatment strategies that capture the diverse genetic and environmental backgrounds of PD patients. This research highlights the need for a shift towards patient-based models and personalized medicine in the battle against PD by potentially revolutionizing the approach to cure PD.

Disclosures: D. You: None. **E. Yang:** None. **Y. Lee:** None. **H. Park:** None. **K. Yoon:** None. **D. Kim:** None. **M.L. Choi:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

Support: Canadian Neurophotonics Platform Viral Vector Core Facility (RRID:SCR_016477)
CIHR Award FBD-181428
CIHR PJT-183760

Title: Exploring the role of Ndufa13 in mitochondrial dysfunction and in selective vulnerability of Aldh1a1+ DA neurons

Authors: *G. SUNG[1,4], C. BOLDUC[2,4], J.-F. POULIN[3,2];
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Abstract: Loss of Dopaminergic (DA) neurons is well documented in Parkinson's Disease (PD), but among these DA neurons, a subset of them expressing ALDH1A1 within the substantia nigra pars compacta (SNc) appear more vulnerable than the rest. This suggests that there are potential molecular determinants contributing to the selective vulnerability. One of the predominant hypotheses in the field is that the mitochondrial health might be involved in the selective vulnerability in these neurons. Recently, conditional deletion of NDUFS2, a protein subunit in the mitochondrial complex I, in the mouse DA neurons, replicated several features of PD

pathology. By contrast, conditional deletion of another complex I protein in DA neurons did not cause a significant neuronal loss. Thus, it is unclear if neurodegeneration results from mitochondrial complex I dysfunction and if ALDH1A1+ DA neurons are particularly vulnerable. To improve our understanding of how complex I disruption contributes to selective vulnerability, we've decided to study another accessory protein NDUFA13, shown to be essential for the stability of complex I formation and electron transport. In this study, we used Dat-Cre mice to remove NDUFA13 in midbrain DA neurons. The homozygous *Ndufa*13 cKO mice failed to gain weight after weaning and were statistically smaller than control 4 weeks after birth. Furthermore, we assessed PD-like behaviour in the wild type, heterozygous and homozygous *Ndufa*13 cKO mice through the rotarod and open-field test at 4 weeks and 6 weeks of age. The rotarod test showed significant motor deficit for the homozygous KO, while the open-field test showed mild motor deficit in the homozygous KO and mild motor enhancement in heterozygous mice. In addition, we observed an important loss of TH+ fibres in the striatum and to a lesser extent, a loss of TH+ cells in the midbrain of homozygous *Ndufa13* cKO mice but not in the other genotypes. Further analysis will determine if the loss of ALDH1A1+ TH cells is accentuated. By studying the selective vulnerability of DA neurons due to mitochondrial dysfunction could help elucidate more specific biochemical pathway within these neurons that make them more vulnerable.

Disclosures: G. Sung: None. **C. Bolduc:** None. **J. Poulin:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.02/C151

Topic: C.03. Parkinson's Disease

Support: MJFF Grant #15288
NIH CoNDA Grant #IP20 GM130447

Title: Increased diapedesis across the blood-brain-barrier and impaired T-cell populations in a pink1/parkin dual knockout rat model of Parkinson's disease

Authors: *L. ESTRELLA, B. LAMBERTY, J. MANGANARO, K. L. STAUCH;
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Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disorder and leading cause of motor disease. This condition is primarily characterized by the death of dopaminergic neurons located in the *Substantia Nigra pars compacta* (SN_{pc}), the loss of corresponding dopaminergic synapses that project towards the Striatum, and the onset of Lewy Bodies made up of aggregated Alpha-Synuclein protein. Another major complication, which is present in multiple neurodegenerative conditions and is thought to contribute to disease progression, is the disruption of the blood-brain-barrier (BBB) integrity and subsequent immune

cell activation from both glial cells and infiltrating peripheral immune cells, like T-Cells. Here, we describe the generation and phenotypic characterization of a combined Pink1/Parkin double knockout (dKO) rat, which reproducibly exhibits PD-relevant abnormalities. Using this model, we further interrogated the immune cell profile from both glial cells, using histological approaches, and peripheral immune cells, from isolated Peripheral Blood Mononuclear Cells (PBMCs) in wildtype and dKO rats. We observed the presence of post-reactive gemistocytic astrocytes in the SN_{pc} of dKO rats at 12 months of age, suggestive of glial immune activation and possible loss of gliovascular supportive interactions. Similarly, a significant increase in T-cell infiltration (diapedesis) across the BBB was found at the Striatum of dKO rats, a synonymous region where Tau and Alpha-Synuclein aggregates were found. Peripheral immune cell profiling via flow cytometry in PBMCs showed altered levels of CD4+ and CD8+ cells, which coincided with disrupted metabolic function by an observed decrease in maximal mitochondrial respiration. In conclusion, we found that abolishing Pink1/Parkin-mediated pathways in rats leads to glial cell activation in the brain, increased diapedesis across the BBB, and significant disruptions in the peripheral immune cell homeostasis. This research highlights the neuroprotective role that Pink1/Parkin-mediated pathways may play against disease progression in neurodegenerative diseases, like PD.

Disclosures: L. Estrella: None. **B. Lamberty:** None. **J. Manganaro:** None. **K.L. Stauch:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.03/C152

Topic: C.03. Parkinson's Disease

Support: R01-NS122226-01

Title: Automated abnormal involuntary movement scoring system using deep learning in a rat model of levodopa-induced dyskinesia

Authors: *C. BUDROW[1], A. JANAPAREDDI[2], A. VELÁZQUEZ[3], F. MANFREDSSON[4], C. M. KELLEY[5], C. R. BISHOP[6];
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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by motor impairment, arising in part through dopamine (DA) neuronal loss within the substantia nigra pars compacta (SNc). While levodopa (L-DOPA) is widely accepted as a gold-standard DA replacement therapy, chronic use results in the development of levodopa-induced dyskinesia

(LID), characterized by debilitating choreic and dystonic movements that plague upwards of 70% of the clinical population. Behaviorally, abnormal involuntary movements (AIMs), characterized by axial, limb and orolingual (ALO) movement features, are pivotal in estimating disease progression and treatment efficacy in preclinical models and within the clinic. While the AIMs rating scale is a reliable assay, scoring requires manual, qualitative observations that are often subject to reduced temporal specificity and inter-rater variability. Alternatively, deep learning models are gaining traction, and when integrated with animal pose estimation (APE), are capable of automating accurate and objective behavioral assessments. However, current models demonstrate variable accuracy and flexibility as a consequence of time-constraint and visual fatigue. In attempts to overcome common barriers in automating dyskinesia scoring, we first compiled a diverse and comprehensive dataset for training deep learning models reliant on APE. To do so, TPH2-Cre+ Long Evans and Sprague Dawley rats (N=29) were rendered hemiparkinsonian via 6-hydroxydopamine (6-OHDA) lesioning to the left medial forebrain bundle (MFB), followed by chronic L-DOPA (6-12 mg/kg, s.c.) treatment, where AIMs were captured by 3 GoPro Hero9 Black cameras positioned 120° around AIMs cylinders at 2 min time-bins, every 10 min, for 120-180 min. Second, we then integrated our dataset into a deep learning model to assess its accuracy in extracting AIM features. To do so, frames were extracted from video recordings of dyskinetic rats in varying lighting and resolution conditions, where frames were segmented into discrete frames and resized to standardized 960 x 540 pixel dimensions repositioned from the DeepLabCut library. Key-feature points were manually annotated for model training purposes. Results demonstrated increasingly promising likelihood scores across subsequent generations in pinpointing AIMs, and with continued training and additional key-feature point extractions, posits clear utility in purposing this model for AIMs scoring in preclinical and clinical assessments of LID.

Disclosures: C. Budrow: None. **A. Janapareddi:** None. **A. Velázquez:** None. **F. Manfredsson:** None. **C.M. Kelley:** None. **C.R. Bishop:** None.

Poster

PSTR452: Parkinson’s Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.04/C153

Topic: C.03. Parkinson’s Disease

Support: MOST 111-2320-B-039 -044 -MY3

Title: Investigating the Therapeutic Efficacy of a Hepatoprotective Natural Product in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-Induced Mouse Model of Parkinson's Disease

Authors: *S.-Y. HUNG;
China Med. Univ., Taichung, Taiwan

Abstract: Oleanolic acid, a natural hepatoprotective compound, possesses antioxidant and immunomodulatory properties. However, its therapeutic effects for Parkinson's disease (PD) remain uncertain. PD is a prevalent neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to striatal dopamine depletion and motor symptoms like resting tremor and bradykinesia. Dysfunction in *PARK7*, the gene encoding the DJ-1 protein, is implicated in autosomal recessive early-onset PD, with DJ-1 crucial for PINK1/parkin-mediated mitophagy. In this study, we investigated the therapeutic efficacy and underlying mechanisms of oleanolic acid in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. Pretreatment with oleanolic acid mitigated PD-associated motor symptoms, reduced nigral dopaminergic neuronal loss, and ameliorated striatal terminal degeneration. Additionally, post-treatment with oleanolic acid alleviated motor deficits, attenuated dopaminergic degeneration in the nigra and striatum, and upregulated Bcl-2 and DJ-1 expression levels. Our findings suggest that oleanolic acid confers neuroprotection in PD by enhancing mitophagy and inhibiting dopaminergic neuronal death, highlighting its potential as a therapeutic agent for PD prevention and treatment.

Disclosures: S. Hung: None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.05/C154

Topic: C.03. Parkinson's Disease

Support: NIH grants NS127391
NIH grants NS129188
Parkinson's Cell Therapy Research Fund at McLean Hospital and Massachusetts General Hospital
Masson Family Endowed Scholar in Neurosurgery

Title: A comparative study of diverse rodent models to assess the efficacy of Parkinson's disease cell replacement therapy

Authors: *J. JEON[1], H. L. RYU[1], Z. SHRESTHA[1], Y. PARK[1,2], Y. HONG[1], B. SONG[3], T. HERRINGTON[4], J. S. SCHWEITZER[3], P. LEBLANC[1], B. CARTER[3], K. S. KIM[1,3]; [1]McLean Hospital/Harvard Med. Sch., Belmont, MA; [2]Dept. of Medicinal & Life Sciences, Ctr. for Bionano Intelligence Educ. and Research, In, Hanyang Univ., Ansan, Korea, Republic of; [3]Neurosurg., [4]Neurol., Harvard Med. Sch., Boston, MA

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of midbrain dopaminergic neurons in the substantia nigra, making cell replacement therapy (CRT) a promising therapeutic approach. To effectively investigate and optimize CRT, it is crucial to establish appropriate and reliable animal models for quantifiable efficacy

measurements. Currently, one of the most widely used models involves athymic rats, where neurotoxin 6-hydroxydopamine (6-OHDA) is stereotaxically injected, typically into the medial forebrain bundle (MFB). This model is preferred for its reliability and efficiency over normal rats, as it eliminates the need for daily immunosuppressant administration. Additionally, immunodeficient mouse models like NSG mice are also employed because they are easier to handle and less expensive. However, comparative studies assessing the effects of different lesion sites and optimization of parameters are lacking. In this study, we systematically compared 6-OHDA lesions in different brain areas (MFB, substantia nigra, and striatum) in NSG mice and compared the outcomes to athymic rats with 6-OHDA lesions in the MFB, following transplantation of midbrain cells derived from human embryonic stem cells and human induced pluripotent stem cells. This comparative analysis aims to provide valuable insights into selecting the most efficient animal model for specific CRT research purposes. By advancing *in vivo* efficacy studies and addressing the comparative effectiveness of rodent models, this research will facilitate the translation of preclinical findings into clinically effective therapies for PD patients, especially in the settings of autologous CRT.

Disclosures: J. Jeon: None. **H.L. Ryu:** None. **Z. Shrestha:** None. **Y. Park:** None. **Y. Hong:** None. **B. Song:** None. **T. Herrington:** None. **J.S. Schweitzer:** None. **P. Leblanc:** None. **B. Carter:** None. **K.S. Kim:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.06/C155

Topic: C.03. Parkinson's Disease

Support: Italian Ministry of Health (RF-2019-12370182)

Title: Environmental enrichments in early and advanced Parkinson's disease: effects on motor, cognitive, and emotional symptoms in a PINK1 mouse model

Authors: *F. BALSAMO[1,2], E. LANDOLFO[2], E. BERRETTA[2], M. MONTANARI[4,3], G. PONTERIO[3], P. BONSI[3], F. GELFO[1,2];
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Abstract: The ability to successfully respond to changing environmental conditions varies among individuals. Various environmental factors can influence both the physiological functions of the central nervous system and its capacity to cope with pathological changes. According to the concept of *cognitive reserve*, the lifelong social, physical, and cognitive experiences can make the brain more resilient to neuronal damage. Parkinson's disease (*PD*) is a progressive neurodegenerative disorder. Early-onset genetic *PD* is frequently linked to the PTEN-induced

putative kinase 1 (*PINK1*) mutation, which results in a gradual loss of physiological functions. While *PD* primarily manifests as a motor disorder, research indicates the presence of non-motor symptoms in its early stages. Notably, cognitive impairment, anxiety, and depression are significant non-motor features of *PD*. The present study aimed to investigate the effects of multimodal and cognitive stimulations on motor performances, cognitive functions, emotional, motivational, and behavioral manifestations in a *PINK1* mouse model of *PD* at early and advanced stages. Male *PINK1* knock-out (*KO*) mice aged 2 and 6 months were compared to *PINK1* wild-type (*WT*) male controls following 4 weeks of exposure to three different environmental conditions: standard condition, cognitive enrichment, and multimodal enrichment. The experimental groups (6 groups, N=12/group) underwent a behavioral assessment battery, including tests for cognitive functions (Novel Object Recognition Test), emotional behaviors (Splash Test, Elevated Plus Maze Test, and Forced Swimming Test), and locomotor capabilities (Rotarod Test). At 2 months, data revealed specific alterations in *KO* mice as regards cognitive and emotional functioning, not accompanied by motor impairment. These alterations included changes in motivational and self-care behavior, novelty recognition memory, and active coping strategies, all of which were alleviated by the exposure to enriched stimulations. By 6 months *KO* mice showed motor and self-care impairments, which were also relieved by enriched stimulations. Cognitive deficits were not significantly evident in *KO* compared to *WT* at this later stage of *PD* progression, likely due to physiological aging in both groups which might overshadow differences, although treatments improved the performance of all groups. These findings support the effectiveness of cognitive and multimodal environmental enrichments as protective treatment strategies to mitigate early cognitive and emotional symptoms during the prodromal stage of *PD*.

Disclosures: F. Balsamo: None. **E. Landolfo:** None. **E. Berretta:** None. **M. Montanari:** None. **G. Ponterio:** None. **P. Bonsi:** None. **F. Gelfo:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.07/C156

Topic: C.03. Parkinson's Disease

Support: Grant #: R01NS109227

Title: The effects of levodopa on skilled reaching in the rat 6-OHDA model of Parkinson Disease

Authors: *J. CHOI[1], M. ROCHLEN[1,4], K. MERCADO-ROSADO[1], K. ULMER[1], H. ZHANG[1], T. FRIEDLANDER[1], S. RAU[1], K. CODEN[1,2], D. K. LEVENTHAL[1,2,3,5];
[1]Dept. of Neurol., [2]Neurosci. Grad. Program, [3]Parkinsons Dis. Res. Ctr. of Excellence, Univ. of Michigan, Ann Arbor, MI; [4]Co-First Author, Ann Arbor, MI; [5]Neurol., VA Ann Arbor Healthcare Syst., Ann Arbor, MI

Abstract: Parkinson's Disease (PD) is characterized by degeneration of nigrostriatal neurons responsible for dopamine production, leading to the motor symptoms of bradykinesia, rigidity, and rest tremor. While dopamine replacement therapy with levodopa effectively mitigates bradykinesia, its impact on coordination is limited. Levodopa increases tonic brain dopamine levels, but likely does not restore normal dynamic dopamine signaling. Hence, we propose that disrupted dopamine dynamics underlie the persistence of coordination deficits despite increased dopamine levels with levodopa treatment. In this study, our goal was to establish a 6-OHDA rat model that recapitulates the disrupted dopa-responsiveness of dexterity in human PD., We assessed skilled-reaching task performance across varying degrees of nigrostriatal degeneration and evaluated the effect of levodopa on forelimb-digit coordination during skilled reaching. Rats with partial 6-OHDA lesions and sham-lesioned controls maintained skilled reaching performance. However, rats with complete hemispheric lesions were impaired in skilled reaching, which was not rescued by levodopa. This preliminary investigation suggests that appropriate 6-OHDA lesions can model the impaired dexterity of PD, setting the stage to study the pathologic basis of impaired dexterity in PD.

Disclosures: J. Choi: None. **M. Rochlen:** None. **K. Mercado-Rosado:** None. **K. Ulmer:** None. **H. Zhang:** None. **T. Friedlander:** None. **S. Rau:** None. **K. Coden:** None. **D.K. Leventhal:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.08/C157

Topic: C.03. Parkinson's Disease

Support: NIH NINDS R01 NS117469

Title: Chronic resveratrol infusion to the lateral periaqueductal gray via stereotaxic microcannulation augments ultrasonic vocalizations and reduces inflammation in male Pink1-/- rats

Authors: S. A. LECHNER, M. HAMZA, D. G. S. BARNETT, ***C. A. KELM-NELSON**; Surgery, Univ. of Wisconsin Madison, Madison, WI

Abstract: Parkinson disease (PD) is a progressive neurodegenerative disorder that affects approximately 10 million people globally. Nearly all PD patients experience debilitating vocal deficits which manifest in the prodromal phase and are refractory to traditional PD therapies. Thus, developing novel treatment strategies to ameliorate prodromal PD pathology in brainstem vocal motor pathways is critical to alleviate or prevent vocal deficits. Using the mitochondrial dysfunction *Pink1*-/- rat to model prodromal PD, our past brainstem transcriptomics and drug repurposing approaches identified resveratrol, an anti-inflammatory phenol, as a top drug candidate to potentially reverse pathologic gene expression and alter PD-like behavior. This was

preliminarily validated in our *Pink1*-/- rat midbrain neuron cell culture work, as resveratrol significantly increases *Snap25* gene expression *in vitro*. Here, we hypothesized that a four-week, site-specific resveratrol infusion into the lateral periaqueductal gray (LPAG) will increase the ultrasonic vocalization intensity, reduce inflammatory gene expression, and increase SNAP-25 expression in the LPAG of male *Pink1*-/- rats compared to wild-type (WT) rats. As PD progression and LPAG projections influence multiple behaviors over time, we quantified at baseline and 4 weeks post-treatment spontaneous limb motor activity and assessment of thermal nociception to test the additional hypotheses that there would not be a rescue of limb-motor deficits caused by canonical dopamine PD pathology and no modulation of nociception from the cannulation procedure. After baseline testing, all rats underwent unilateral stereotaxic implantation of a glass microcannula targeting the LPAG through which resveratrol was administered via a subcutaneous osmotic pump (0.03 mg/ml at 0.11 µl/h). Following four-weeks of infusion, all rats underwent final behavioral testing and tissue collection. The QIAGEN RT^2 Profiler PCR array for NF-κB pathway targets quantified differentially regulated inflammatory genes in whole blood. All rats produced more vocalizations, and WT, but not *Pink1*-/- rats, significantly increased call intensity (louder) post-treatment. *Pink1*-/- rats moved less than WT, consistent with observations from our past work. Nociception was unaffected, which corroborated cannula placement and minimal off-target effects. PCR array showed downregulated systemic inflammation markers *Cd40*, *Cd74*, and *Cd83* in *Pink1*-/- rats relative to WT. LPAG *in situ* analysis for *Snap25* is ongoing. This study is the first to demonstrate that site-specific resveratrol administration into the LPAG increases vocal intensity in the rat.

Disclosures: S.A. Lechner: None. **M. Hamza:** None. **D.G.S. Barnett:** None. **C.A. Kelm-Nelson:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.09/C158

Topic: C.03. Parkinson's Disease

Title: Studying the neuroprotective effect of Turmeric (curcuma longa) in Parkinson's disease

Authors: *V. SARKISIAN[1], N. BEHNAM DEHKORDI[2];
[1]Orbeli Inst. Physiol, Yerevan, Armenia; [2]Laorbli Inst. of Physiol., Natl. Acad. of Sci. Republic of Armenia, Yerevan, Armenia

Abstract: Studying the neuroprotective effect of Turmeric (curcuma longa) in Parkinson's disease
Turmeric (Curcuma longa) has a therapeutic effect on the brain. It modulates neurotransmitters, increases brain serotonin and norepinephrine levels, while decreasing acetyl cholinesterase activity. The antioxidant properties of turmeric are a promising option for preventing the adverse effects of rotenone, especially by protecting cells against oxidative stress and related damage. In

our investigation of the potential neuroprotective effects of turmeric against rotenone-induced neurotoxicity, we chose to administer curcumin (the active ingredient of turmeric) through intraperitoneal injection in rats. The present study aims to provide new evidence for the validity of the rotenone rat model of PD by investigating whether neuronal activity in the hippocampus is altered, as well as to determine the neuroprotective properties of turmeric. Male albino rats were infected with rotenone injections (2.5 mg/ml i.p.) for 21 days. In a PD model, the effects of turmeric and curcumin (200 mg/kg) on electrophysiological and behavioral parameters were investigated. Rotenone-induced changes in locomotor activity were assessed using the cylinder test. Rotenone causes a significant decrease in hippocampus neuronal activity. The results suggest that turmeric and curcumin can improve movement disorders and electrophysiological parameters and be useful in the treatment of PD. This study provides significant insights into the potential of turmeric to mitigate the detrimental effects of rotenone on the brain, particularly in the hippocampus region, suggesting its possible implications for the treatment of neurological disorders related to rotenone exposure.Keywords: Parkinson's disease, turmeric, rotenone, neuroprotection, behavior

Disclosures: V. Sarkisian: None. **N. Behnam Dehkordi:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.10/C159

Topic: C.03. Parkinson's Disease

Support: ZIA-ES103310
ZIA-AG000944

Title: Dietary Nicotinamide Riboside alleviates motor symptoms in a mouse model of Parkinson's disease

Authors: *S. SAHA[1], C. MENG[1], J. DONG[2], J. ZHOU[3], A. PAPANERI[1], L. SUN[2], H. CAI[2], G. CUI[1];
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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder featuring the progressive loss of nigral dopamine (DA) neurons and a cohort of motor and non-motor symptoms. Aging and environmental exposure-induced mitochondrial dysfunction is believed to be one of main mechanisms underlying the neurodegeneration. Nicotinamide riboside (NR), a nicotinamide adenine dinucleotide (NAD+) precursor, is a dietary supplement that has been suggested to be beneficial to cellular health via promoting mitochondrial function, biogenesis, and conversion of nutrients to energy. Nevertheless, it's still unknown whether dietary NR is beneficial in reducing the risk or mitigating the symptoms of PD. We tested this by using a "double-hit" PD mouse

model having both genetic and environmental avenues of causality, by overexpressing α-synuclein A53T in substantia nigra pars compacta (SNc) DA neurons (genetic hit) and by exposing the mice to fungicide benomyl via diet (environmental hit). Longitudinal behavior analysis revealed that chronic NR supplementation via drinking water rescued the motor deficits in PD mice both in rotarod and open field tests but did not rescue the loss of DA neurons. In vivo fiber photometry measurements of the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio using the genetically encoded fluorescent ratiometric sensor, PercevalHR, showed that NR increased the ATP/ADP ratio in multiple types of neurons in the brain. Our study of DA release using genetically encoded fluorescent sensors tagged with control fluorophore exhibited that NR elevated the levels of tonic and evoked DA release in the striatum of control mice as well as PD model mice. These results suggest that NR treatment improves the overall mitochondrial function in neurons and promotes DA release, which may provide beneficial effects in PD patients.

Disclosures: S. Saha: None. **C. Meng:** None. **J. Dong:** None. **J. Zhou:** None. **A. Papaneri:** None. **L. Sun:** None. **H. Cai:** None. **G. Cui:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.11/C160

Topic: C.03. Parkinson's Disease

Support: NIH R56 NS109608
R01 NS122805
ADHS18-198846

Title: Evaluating sex-specificity in the activity of sub-anesthetic ketamine to attenuate L-DOPA-induced dyskinesia

Authors: *R. PARMAR[1], C. STOPERA[2], T. FALK[3];
[1]Univ. of Arizona, Tucson, AZ; [2]Neurosci., The Univ. of Arizona, Tucson, AZ; [3]Dept. Of Neurol., Univ. of Arizona, Tucson, AZ

Abstract: Parkinson's disease (PD) is a common and disabling neurodegenerative condition. It often starts subtly with symptoms like depression and sleep disturbances. However, by the time hallmark symptoms such as tremors and rigidity appear, significant damage to dopamine-producing neurons has already occurred. Current treatment, Levodopa (L-DOPA), helps manage motor symptoms but doesn't address non-motor symptoms or slow disease progression. Moreover, long-term L-DOPA use often leads to L-DOPA-induced dyskinesia (LID), a severe side effect affecting more than 90% of patients. We have previously demonstrated that treatment with sub-anesthetic ketamine (10-hrs; 5 x 20 mg/kg; *i.p.*; 2-hrs apart) can reduce established and attenuate development of LID in 6-hydroxydopamine (6-OHDA)-lesioned male Sprague-Dawley

rats and is acutely antiparkinsonian. Yet, given the known sex-specificity reported for ketamine treatment in depression and alcohol dependence models it is vital to replicate our previous data in female PD rats to uncover any sex-specific differences. This study aims to advance our understanding by investigating whether ketamine can mitigate or prevent LID in female PD rats. In a LID development model, we divided the female PD rats into two groups: a vehicle group (n=6) and a ketamine group (n=8). Female Sprague-Dawley rats with unilateral 6-OHDA lesions (medial forebrain bundle injection) underwent a ketamine (20 mg/kg) or saline regimen administered over 10-hrs (5 *i.p.* injections; 2-hrs apart), followed by immediate L-DOPA treatment to assess Abnormal Involuntary Movements (AIMs) once per week. Concurrently, female rats received daily L-DOPA injections, starting with 6 mg/kg for Days 0-13 and increasing to 12 mg/kg for Days 14-28. AIMs were evaluated every 3-4 days for 28 days. Preliminary findings show, though not statistically significant (Mann-Whitney tests), the ketamine group had a ~15% decrease in LID compared to the vehicle group on treatment days 14 and 21. Given that in the males, the same 20 mg/kg ketamine 10-hrs dosing paradigm led to a significant ~50% reduction of development of LID this suggests a potential sex-specific ketamine dose requirement, with females needing a higher dose for significant LID reduction. *Post hoc* evaluation of striatal tyrosine hydroxylase (TH) and striatal mTOR levels is ongoing. Next steps involve a dose-response study in females using 20, 25 and 30 mg/kg doses to determine the optimal ketamine dosage in models of both established LID and development of LID. This approach is crucial to enable us to determine the optimal dosage of ketamine necessary to achieve a significant reduction in LID in the female rat model of PD.

Disclosures: R. Parmar: None. **C. Stopera:** None. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TF has a patent for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease, licensed to PharmaTher Inc., consulted, travel support from PharmaTher.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

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Program #/Poster #: PSTR452.12/D1

Topic: C.03. Parkinson's Disease

Support: CONAHCYT CF 2023-G 597

Title: Exploring the interaction of Cannabidiol and Lysophosphatidylinositol with the GPR55 receptor through in silico and immunohistochemical analyses

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Abstract: Cannabidiol (CBD) presents antiparkinsonian properties and neuromodulatory effects, possibly due to the pleiotropic activity caused at multiple molecular targets. Recently, the GPR55 receptor has emerged as a molecular target of CBD and lysophosphatidylinositol (LPI). Interestingly, GPR55 mRNA is expressed in the external globus pallidus (GPe) and striatum, areas affected by dysfunction in Parkinson's disease (PD). This study aims to evaluate the alterations in the expression of GPR55 and GAD67 in hemiparkinsonian rats and to validate their interactions using molecular docking techniques. The hemiparkinsonism animal model was established by inducing a lesion in male Wistar rats via stereotaxic surgery, utilizing the neurotoxic 6-hydroxydopamine (6-OHDA) infused into the nigro-striatal pathway. Following a twenty-eight-day period, lysophosphatidylinositol (LPI) or CBD was administered daily for three consecutive days (days 28 to 30 post-injury). Computational methods were then employed for in silico analysis to investigate the receptor binding sites and interactions of CBD and LPI on the GPR55 receptor. Results indicated a reduction in immunoreactivity levels for the GPR55 receptor in the globus pallidus in the 6-OHDA model, with significant recovery observed following CBD administration. Additionally, differences in immunoreactivity for the GAD-67 enzyme were observed in the striatum and ipsilateral GPe among CBD-treated, 6-OHDA-lesioned, and LPI-treated rats. At the *in silico* level, molecular docking revealed consistent interactions, highlighting the involvement of amino acid regions Lys167 and Glu98, along with the interaction of the three drugs at the orthosteric site of the receptor. These results suggest that the inhibitory effects of CBD on the GPR55 receptor in the GPe may correlate with GABAergic overactivation in hemiparkinsonism. This sheds light on new perspectives for comprehending the cellular-level disruptions witnessed in the striatum and GPe in Parkinson's disease models.

Disclosures: F. Patricio Martínez: None. **E. Morales Dávila:** None. **A. Patricio-Martínez:** None. **J. Perez-Aguilar:** None. **I.D. Limon Perez De Leon:** None.

Poster

PSTR452: Parkinson’s Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.13/D2

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS R01NS119610-01
MJFF019068

Title: Investigating the neuroprotective role of peripheral NK cells in a mouse model of Parkinson's disease

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Abstract: INVESTIGATING THE NEUROPROTECTIVE ROLE OF PERIPHERAL NK CELLS IN A MOUSE MODEL OF PARKINSON'S DISEASE.Adetutu Adebowale, Jae-Kyung Lee Department of Physiology and Pharmacology, University of Georgia College of Veterinary Medicine.
Disclosures**Adetutu Adebowale**: None. **Jae-Kyung Lee**: None.
ABSTRACT
Natural killer (NK) cells are critical components of the innate immune system with unique ability to recognize and eliminate virally infected and transformed cells. The activities of NK cells are tightly regulated by a variety of receptors that recognize specific ligands which are expressed on target cells. Some of these receptors are activating such as NCRs (Natural Cytotoxicity Receptors), inhibitory such as NKG2A and chemokine receptors such as CX3CR1. Our previous study has uncovered the neuroprotective role of NK cells in a mouse model of Parkinson's disease (PD) induced by preformed fibril (PFF) α-synuclein. However, it remains unclear whether NK cells exert their neuroprotection in the periphery or if they migrate to the CNS. To investigate if NK cells trafficking to the CNS is required for neuroprotection, we aimed to generate a new transgenic mouse whose NK cells lack CX3CR1, a chemokine receptor expressed on NK cells, which has been reported to modulate recruitment and migration of NK cells. To achieve this, we utilized NK cell specific NCR1-Cre line obtained from INSERM (France). We have successfully generated a floxed mouse strain to create NK-specific CX3CR1 knockout (KO) mice. First, to determine the specificity of NCR1-dependent Cre recombination, we crossed NCR1-iCre line with R26R-EYFP mice. Flow cytometry data showed that EYFP was expressed on NCR+ NK cells but not on B cells, T cells or Monocytes in the spleen and blood of NCR1-ROSA Transgenic mice.Next, we crossed NCR1-cre mice and CX3CR1 floxed mice. We performed flow cytometry analysis and validated the specific CX3CR1 expressions on various immune cell types including NK cells and confirmed that we achieved conditional depletion of CX3CR1 on NK cells. Notably, analysis of our data confirmed that CX3CR1 conditional knock out alters NK cell maturation. In future study, we are planning to utilize this mouse model by inducing PD with preformed fibril (PFF) α-synuclein to determine whether CX3CR1 is required for the infiltration of NK cells into the brain in a preclinical mouse model of PD.

Disclosures: A.A. Adebowale: None. **J. Lee:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.14/D3

Topic: C.03. Parkinson's Disease

Support: ASAP-020505

Title: Temporal development of functional alterations of midbrain dopaminergic neurons by transgenic expression of neuromelanin in a parkinson's disease mouse model

Authors: *B. ZARRILLI[1,2,3], C. GIACOMET[1,2,3], F. COSSA[1,2,3], M. MASSARO CENERE[2,3], M. FEDERICI[2,3], M. VILA[3,4], E. GUATTEO[2,3,5], N. BERRETTA[2,3], N. B. MERCURI[2,3,1]; [1]Univ. of Rome "Tor vergata", Roma, Italy; [2]IRCCS Fondazione Santa Lucia, Rome, Italy; [3]Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Washington, DC; [4]Vall d'Hebron Res. Inst., Barcelona, Spain; [5]Dept. of Movement Sci. and Wellness, Parthenope Univ. of Naples, Naples, Italy

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease. Accumulation of neuromelanin (NM) in dopamine (DA)-releasing neurons of the substantia nigra pars compacta (SNpc) may be the cause of their degeneration, leading to typical PD symptoms. To investigate the temporal development of dysfunctions in the ventral midbrain, we used patch-clamp recordings from horizontal midbrain slices to evaluate passive and active properties of SNpc DA neurons in Tg-TH-hTyr (hTyr) mice expressing the human melanin-producing enzyme tyrosinase in catecholaminergic neurons, at 6-7 and 15-17 months. These mice express high levels of NM, appearing as intracellular and extracellular granules in the ventral midbrain. We identified presumed DA neurons based on electrophysiological hallmarks like prominent outward current following a strong depolarizing step (I_{AHP}) and a hyperpolarization-activated inward current (I_h).Significant differences were found exclusively in the DA neurons' population of hTyr at both 6-7 and 15-17 months, expressed as higher firing rate in response to depolarizing steps. This enhanced neuronal excitability was associated with a significantly smaller I_{AHP} and I_h only in 6-7 months old hTyr mice.In conclusion, our data indicate that NM accumulation leads to higher excitability of the DA neurons' population at both ages, although at 15-17 months, neurons paradoxically present fewer signs of functional alteration. We propose that at 6-7 months, the population of DA neurons present functionally active neurons, which will later be lost, so that at 15-17 months, only neurons somehow more resistant to NM accumulation are recorded.

Disclosures: B. Zarrilli: None. **C. Giacomet:** None. **F. Cossa:** None. **M. Massaro Cenere:** None. **M. Federici:** None. **M. Vila:** None. **E. Guatteo:** None. **N. Berretta:** None. **N.B. Mercuri:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.15/D4

Topic: C.03. Parkinson's Disease

Support: ASAP-020505

Title: Age dependent alterations in cortico striatal synaptic plasticity of transgenic mice expressing neuromelanin

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Abstract: Among the neurodegenerative diseases Parkinson's Disease (PD) is one of the most common. It's been suggested that accumulation of neuromelanin (NM) in dopamine (DA)-releasing neurons of the substantia nigra may be the cause of their degeneration, thereby reducing DA release in target areas like the striatum.In view of its well-known dependence on the DA signal, we investigated possible alterations of synaptic plasticity in the striatum of Tg-TH-hTyr (hTyr) mice. These mice express the human tyrosinase enzyme inducing the production of NM in catecholaminergic neurons. Extracellular recordings were performed on striatal slices to measure synaptic plasticity of the cortico-striatal input. Induction of long-term depression (LTD) was defined as reduction of the synaptic response by at least 20% relative to control, 1h after the conditioning train.In 6-7-month-old wild type (WT) mice LTD was induced in all recorded slices, while in 15-17-moths old WT mice the same protocol did not always induce synaptic plasticity. Moreover, when LTD was induced, the degree of depression was higher in 6-7 than in 15-17 months old mice.In hTyr we still observed a similar difference in the degree of depression between 6-7- and 15-17-months old mice, however, LTD was less pronounced that in WT at both ages.In conclusion, cortico-striatal plasticity is subject to an age-dependent physiological reduction, however, NM accumulation leads to an acceleration of this process, exacerbating the loss of cortico-striatal synaptic plasticity at younger age, possibly for a reduction in the efficacy of the DAergic input.

Disclosures: C. Giacomet: None. **B. Zarrilli:** None. **F. Cossa:** None. **M. Massaro Cenere:** None. **M. Federici:** None. **M. Vila:** None. **E. Guatteo:** None. **N. Berretta:** None. **N.B. Mercuri:** None.

Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.16/D5

Topic: C.03. Parkinson's Disease

Support: Health Research BC / Parkinson Society BC Research Trainee Award RT-2023-3277
Parkinson Society Canada Pilot Project Grant PPG-2022-0000000083

Title: Exploring the interplay between SARS-CoV-2 infection and early Parkinson's disease pathology in K18-hACE2 male and female mice.

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Abstract: Exposure to environmental agents, including viral infection, increases vulnerability to Parkinson's disease (PD), but COVID-19 neurodegenerative risk's extent is unknown. We studied a plausible link between SARS-CoV-2 infection and susceptibility to PD in transgenic mice expressing the human receptor angiotensin-converting enzyme 2 (K18-hACE2). We investigated a two-hit model with a moderate (10 mg/kg) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) dose, recapitulating early PD, and subsequent mild COVID-19 ($2.5x10^3$ $TCID_{50}$ of Canadian WT SARS-COV-2 strain) 11 days post-MPTP in male and female K18-hACE2 mice. On day 5 post-infection (dpi), viral titer was evaluated while morbidity and survival were monitored for 14 days. We measured striatal dopamine (DA) and its metabolites (DOPAC, 3-MT, HVA) contents by HPLC. We examined microglia and astrocyte reactivity with IBA1 and GFAP labelling in the substantia nigra pars compacta (SNpc). DA SNpc neurons were assessed with tyrosine hydroxylase (TH)-immunoreactive cell counts. SARS-CoV-2 caused a progressive weight loss in male and female mice until day 4. In SARS-CoV-2-infected mice, viral titers in nasal turbinates and brain were similar in both sexes, but females had higher pulmonary viral load than males. SARS-CoV-2 did not affect striatal DA and its metabolites in both sexes. MPTP-induced decrease of striatal DA content in mice with or without SARS-CoV-2 infection was similar, but males showed a marked reduction compared to females. SARS-CoV-2 aggravated the MPTP-mediated reduction of DOPAC, 3-MT, and HVA in co-exposed males, while there was no effect on DA metabolites in females. Co-exposed male mice had an increase in DA turnover, to a lesser extent compared to MPTP whereas female MPTP+SARS-CoV-2 mice had a marginal increase only in HVA/DA ratio. MPTP and/or SARS-CoV-2 exposure enhanced glial reactivity compared to control. Co-exposed mice showed robust GFAP and IBA1 reactivity in the SNpc of males higher than their individual effects; SARS-CoV-2 alone showed a small increase in GFAP compared to MPTP. In females the single or dual exposure had no outcome on IBA1. Only the MPTP+SARS-CoV-2 group showed robust GFAP reactivity compared to control and SARS-CoV-2 groups. No neurodegeneration was measured in females across groups whereas TH-immunoreactive cells in males were lowest in the MPTP+SARS-CoV-2. The present data shows in MPTP mice that COVID-19 aggravates DA metabolic dysregulation and loss/impairment of brain DA neurons with more inflammation than either MPTP or COVID-19 single exposure. This supports the likelihood of accelerated progression of prodromal PD due to widespread COVID-19.

Disclosures: I.O. Awogbindin: None. **M. Bourque:** None. **M. Morissette:** None. **C. Rheaume:** None. **M. Hamelin:** None. **G. Boivin:** None. **M. Tremblay:** None. **T.P. DiPaolo:** None.

Poster

PSTR452: Parkinson’s Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.17/D6

Topic: C.03. Parkinson’s Disease

Support: F31NS115524

Title: Phenotypic characterizations of a dopamine neuron subtype-specific ablation model of Parkinson's Disease

Authors: *Z. GAERTNER[1], N. LOPEZ GONZALEZ DEL REY[2], R. AWATRAMANI[1]; [1]Northwestern Univ., Chicago, IL; [2]Neurol., Feinberg Sch. of Med., Northwestern Univ., Chicago, IL

Abstract: Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). However, many studies have reported selective vulnerability of specific subpopulations of DA neurons, as defined by their anatomical locations, projection patterns, or expression patterns of marker genes. One such subtype that has been the subject of several recent studies is cells expressing the transcription factor Sox6. Post-mitotic expression of this marker within the SNc selectively labels ventral tier neurons, and that these cells degenerate more than other DA neurons in PD and mouse models. Here, we utilized an intersectional genetic strategy to selectively ablate Sox6+ DA neurons in mice and characterized the ablation and behavioral deficits through several common motor paradigms, as well as deep learning-based tracking of spontaneous behaviors in an open field. Sox6-ablated mice show loss of ventral SNc and corresponding denervation of the dorsal striatum, but sparing of ventral and caudal striatal DA axons, mimicking human PD pathology. Interestingly, the mice display a progressive parkinsonian phenotype despite complete ablation early in the mouse's lifespan. These deficits are observed across several paradigms of both raw motor abilities and motor learning. Sox6-ablated mice also show selective loss of dopaminergic projections to the dorsolateral striatum with no apparent compensation from other DA subtypes at any age. Overall, these results suggest that Sox6+ DA neurons encompass a vital population driving PD motor symptom pathology and that this model can serve as a valuable resource for studying circuit-level PD pathophysiology.

Disclosures: Z. Gaertner: None. **N. Lopez Gonzalez del Rey:** None. **R. Awatramani:** None.

Poster

PSTR452: Parkinson’s Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.18/D7

Topic: C.03. Parkinson's Disease

Support: COMECyT FICDTEM-2021-066
PAPIIT-DGAPA IN216821

Title: Perturbations in mitochondrial activity, ultrastructure, and fission proteins in the manganese model of Parkinson's disease

Authors: *C. GARCIA-CABALLERO[1], J. L. ORDONEZ LIBRADO[2], B. DOMINGUEZ-RODRÍGUEZ[3], E. VELASCO-MENDOZA[3], A. DE ALBA-RÍOS[4], E. MONTIEL-FLORES, Sr.[5], O. APARICIO-TREJO[6], F. GARCIA ARROYO[7], J. PEDRAZA CHAVERRI[3], L. REYNOSO-ERAZO[8], M. AVILA-COSTA[9];
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Abstract: The increasing global lifespan has contributed to a growing incidence of Parkinson's disease (PD) worldwide, presenting a significant health challenge. Despite this, the precise mechanisms underlying neuronal injury remain elusive, necessitating the development of new animal models that reproduce most features of this disorder.
In our laboratory, we developed a rodent model using manganese chloride ($MnCl_2$) and manganese acetate ($Mn(OAC)_3$). This model has demonstrated depletion of substantia nigra compacta dopaminergic neurons, the exposed animals have shown tremor, rigidity, and bradykinesia. These changes were gradual and bilateral, consistent with what has been reported in PD patients.
Our study aimed to explore mitochondrial activity in substantia nigra, striatum, and globus pallidus. Additionally, we evaluate the ultrastructural features of mitochondria and their cristae, and mitochondrial fission proteins. To achieve this, we used male CD1 mice divided into two groups; a) mice that inhaled deionized water (n=20) and b) mice that inhaled ($MnCl_2$)/($Mn(OAC)_3$) (n=20), one hour, two times a week over five months.
We found that inhalation of the Mn mixture induced hypoactivity in complexes I and IV across all structures, particularly in the substantia nigra pars compacta. Furthermore, manganese exposure increased the number of mitochondria and their area but decreased mitochondrial circularity. Likewise, it intensified the occurrence of damaged cristae in the three analyzed nuclei. Finally, it enhanced the expression of Drp1 and Fis1 in the experimental group.
In conclusion, the PD model by manganese mixture inhalation emerges as a valuable tool for analyzing this pathology, successfully replicating specific mitochondrial injuries observed in PD patients. These findings contribute to a deeper understanding of PD's mechanisms and provide a foundation for further mitochondrial investigations and therapeutic interventions.

Disclosures: C. Garcia-Caballero: None. **J.L. Ordonez Librado:** None. **B. Dominguez-Rodríguez:** None. **E. Velasco-Mendoza:** None. **A. De Alba-Ríos:** None. **E. Montiel-Flores:**

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Poster

PSTR452: Parkinson's Disease: Strategies for Modifying Disease Phenotypes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR452.19/D8

Topic: C.03. Parkinson's Disease

Title: Neurological Studies Utilizing Magnetogenetics with Structurally Modified Piezo1 for AAV Delivery

Authors: *Y. LEE[1], W. SHIN[1], M. KWAK[1], L. JAE HYUN[1], J. CHEON[2];
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Abstract: Our research focuses on utilizing the mechanosensitive cation membrane channel, Piezo1, for various applications. Piezo1 can selectively bind to magnetic nanoparticles through antibody-antigen binding, and upon activation by a rotating magnetic field, induces cellular stimulation, a technique known as magnetogenetics (MG). The calcium influx induced by MG stimulation enables temporal and spatial control of neuron firing, offering wireless, long-range, and long-term stimulation capabilities. Using MG-Deep Brain Stimulation, we confirmed increased motor function, sustained symptom relief, and altered neural coherence in a Parkinson's disease model mouse.
However, Piezo1, the largest existing ion channel, faces challenges in gene delivery using adeno-associated virus (AAV), limiting its long-term expression and clinical utility. To overcome this limitation, we introduced a split Piezo1 system, dividing the Piezo1 sequence into two segments for co-expression, and further enabled AAV delivery by deleting the Transmembrane Helical Unit within the Piezo1 structure.
These structural and transcriptional modifications of Piezo1 have enabled AAV delivery, thereby facilitating neural circuit research using MG technology and clinical applications for neurodegenerative disorders.

Disclosures: Y. Lee: None. **W. Shin:** None. **M. Kwak:** None. **L. Jae hyun:** None. **J. Cheon:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.01/D11

Topic: C.03. Parkinson's Disease

Title: Cola acuminata extract inhibition of NLRP3 inflammasome in THP-1 cells as a potential treatment option for Parkinson disease

Authors: *V. NGOUNGOURE NDAM[1], V. OWONA AYISSI[2];
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Abstract: Effect of Cola acuminata extract on the NLRP3 inflammasome activation using THP-1 cells: implications for Parkinson DiseasePersistent chronic neuroinflammation leading to immune system activation is a clinical feature of Parkinson disease. Moreover, inflammasome proteins activation is associated with worsening PD. Therefore, targeting inflammasome proteins may be a promising trail for PD treatment. In this article, Cola acuminata, a plant used in Cameroon to heal neurological diseases was tested on NLRP3 inflammasome inhibition following LPS stimulation using THP-1 cell lines. MTT assay showed that neither the extract nor LPS were cytotoxic to the cells *in vitro* at the concentrations tested. Anti-inflammatory activity was confirmed by significant inhibition of proinflammatory cytokine release following inflammasome activation including IL1β, IL18 and TNFα. This inhibition of inflammasome components was confirmed at the gene and protein levels using RTqPCR and western blot analysis for NLRP3, caspase 1, IL1β and NFkB respectively. Amyloid beta phagocytosis assay showed that the extract at 100 µg/ml increased phagocytosis activity of macrophage cells and the analysis of inflammasome using immunofluorescence showed that cola acuminata barks extract disintegrates inflammasome complex following activation with LPS and Nigericin. Altogether, our finding for the first time describes a promising role of cola acuminata barks extract in preventing inflammasome activation and protection against neuroinflammation which is a key factor in PD development, and that further analysis of this extract is a potential way forward against Parkinson disease.
Key words: NLRP3, neuroinflammation, cola acuminata, THP-1 cells, Parkinson disease

Disclosures: V. Ngoungoure Ndam: None. **V. Owona ayissi:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.02/D12

Topic: C.03. Parkinson's Disease

Support: National Research Foundation (NRF), funded by the Korean Government (MSIT) (2020M3E5D9080660)

Title: Immunization Effects of a Novel α-Synuclein-Based Peptide Epitope Vaccine in Parkinson's Disease-Associated Pathology

Authors: J. PARK[1], K. CHOE[1,2], M. KANG[1], R. AHMAD[1], H. PARK[3], T. PARK[4], ***M. KIM**[1]; [1]Gyeongsang Natl. Univ., Jinju, Korea, Republic of; [2]Dept. of Psychiatry and Neuropsychology, Sch. for Mental Hlth. and Neurosci. (MHeNs), Maastricht Univ., 6229 ER Maastricht, Netherlands; [3]Dept. of Pediatrics, Maastricht Univ. Med. Ctr., Maastricht Univ. Med. Ctr., 6202 AZ Maastricht, Netherlands; [4]Univ. of Glasgow, Glasgow G12 0ZD, United Kingdom

Abstract: Parkinson's disease (PD) is a chronic neurodegenerative disease that affects the central nervous system, specifically the motor system. It is mainly caused by the loss of dopamine due to the accumulation of α-synuclein (α-syn) protein in the striatum and substantia nigra pars compacta (SNpc). Previous studies have reported that immunization may be a potential preventive strategy for neurodegenerative diseases such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Therefore, the aim of the study was to design an α-syn specific epitope vaccine and investigate its effect in PD-related pathophysiology using an α-syn-induced mouse model. We used an in silico model to identify and design a non-toxic α-syn-based peptide epitope vaccine and, to overcome poor immunogenicity, the vaccine was coupled with immunogenic carrier proteins, i.e., ovalbumin (OVA) and keyhole limpet haemocyanin (KLH). Our results showed that vaccinated PD mouse models, especially with vaccines with carrier proteins, improved in motor functions compared with the non-vaccinated PD model. Additionally, the vaccinated groups showed increased immunoglobulin G (IgG) levels in the spleen and plasma as well as decreased interleukin-10 (IL-10) levels in the plasma. Furthermore, vaccinated groups, especially OVA and KLH groups, showed decrease in α-syn levels and increased dopamine-related markers, i.e., tyrosine hydroxylase (TH), vesicle monoamine transporter 2 (VMAT2), and dopamine transporter (DAT), and autophagy activities in the striatum and SNpc. Lastly, our data showed decreased neuroinflammation by reducing the activation of microglia and astrocytes and pro-inflammatory cytokines in the immunized groups, especially with OVA and KLH carrier proteins. Overall, these results suggest that vaccination, especially with immunogenic carrier proteins, is effective in reducing the accumulation of α-syn aggregates in the brain and ameliorate PD-related pathophysiology. Hence, further development of this approach might have a potential role in preventing the development of PD.

Disclosures: J. Park: None. **K. Choe:** None. **M. Kang:** None. **R. Ahmad:** None. **H. Park:** None. **T. Park:** None. **M. Kim:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.03/D13

Topic: C.03. Parkinson's Disease

Title: Development and validation of TRPML1 assays on automated patch clamp platforms

Authors: *D. R. P. SAUTER[1], A. STEINER[2], A. JHA[3];
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Abstract: TRPML1 is a cation-selective ion channel that is ubiquitously expressed in lysosomes and late endosomes. TRPML1 is intimately involved in the regulation of lysosomal Ca2+ homeostasis and is consequently a critical component of autophagy and lysosomal biogenesis. Malfunction of these processes are linked to various neurodegenerative disorders including Alzheimer`s and Parkinson`s disease. The relevance of TRPML1 in neurodegenerative disorders is further validated by a loss-of-function mutation that was shown to cause the neurodegenerative lysosomal storage disease mucolipidosis type IV (MLIV). The patch clamp technique remains the gold standard for studying ion channels as recordings provide a direct measure of the protein's activity. Whilst powerful, the conventional patch clamp method requires highly trained scientists and allows only a low throughput. Automated patch clamp systems have evolved to overcome these limitations and these platforms are therefore well-suited to test large numbers of compounds in a short time to support ion channel drug development programs. Here, an automated patch clamp assay for TRPML1 recombinantly expressed in HEK293 cells is presented. To achieve plasma membrane expression, the two dileucine motifs ($_{15}$LL and $_{577}$LL) of mouse TRPML1 responsible for lysosomal targeting were replaced with alanines to allow trafficking to the plasma membrane. Biophysical characterization of the channel in the whole-cell configuration was in good agreement with the literature. Application of the tool compound ML-SA5 at pH4.6 resulted in a marked increase in current amplitude with EC50 = 3.4 µM. In conclusion, the developed assay allows to record a large number of compounds in a short timespan to identify novel modulators of the TRPML1 channel.

Disclosures: D.R.P. Sauter: A. Employment/Salary (full or part-time):; Sophion Bioscience. **A. Steiner:** A. Employment/Salary (full or part-time):; Casma Therapeutics. **A. Jha:** A. Employment/Salary (full or part-time):; Casma Therapeutics.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.04/D14

Topic: C.03. Parkinson's Disease

Title: Developing new drugs targeting TRPML1 to activate autophagy for the treatment of Parkinson's disease

Authors: *E. PARK;
Threebrooks Therapeut. Inc, Pohang-si, Gyeongsangbuk-do, Korea, Republic of

Abstract: Parkinson's disease is the second most common neurodegenerative disorder after dementia. Typically, symptoms arise around age 60, affecting about 1% of the population. In

2013, the Parkinson's market was worth $3.5 billion, projected to grow at 15% annually, reaching $6.1 billion by 2026. Current treatments primarily focus on dopamine replacement therapy, but long-term usage can lead to side effects, necessitating more fundamental approaches. Recent research has focused on the accumulation of α-synuclein protein as a key factor. Antibodies targeting α-synuclein are actively being developed; however, clinical outcomes are unclear. Autophagy and lysosomes are gaining traction for α-synuclein clearance. Lysosomes, responsible for cellular waste breakdown, play a vital role in neurodegenerative diseases like Parkinson's. Dysfunctions in lysosomal function are linked to various disorders, including Parkinson's. TRPML1, a lysosomal ion channel, is crucial for autophagy/lysosomal regulation, with its activation reducing α-synuclein. We identified a small molecule via screening that activates TRPML1, leading to reduced α-synuclein levels through autophagy induction. Our research promises to be a significant breakthrough in Parkinson's treatment, paving the way for new therapeutic avenues.

Disclosures: E. Park: None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.05/D15

Topic: C.03. Parkinson’s Disease

Title: In vitro differentiation of dopaminergic neurons from human ESC: Parkinson’s disease in vitro model

Authors: M. BSIBSI[1], *M. ZANELLA[1], C. GOMEZ-PUERTO[1], C. VAN DEN BERG[1], B. GÜRKAN[1], K. LO[1], D. KETSKEMETY[1], S. VERMOND[1], A. K. CHOUHAN[2], D. MAGNANI[2], C. LOOMANS[1], S. KOSTENSE[1], M. VLAMING[1], D. F. FISCHER[3]; [1]Charles River Lab., Leiden, Netherlands; [2]Charles River Lab., Saffron Walden, United Kingdom; [3]Charles River, Saffron Walden.

Abstract: Dopaminergic neurons are the main source of dopamine in the mammalian central nervous system and play an important role in multiple brain functions including voluntary movement and many behavioral processes. The loss of dopaminergic neurons is associated with one of the most prominent human neurological disorders, Parkinson’s disease. Therefore, dopaminergic neurons are considered a potential therapeutic target to treat the disease. Charles River has optimized and implemented a robust dopaminergic neuron differentiation protocol that is amenable to compound screening. We generated human embryonic stem cell derived dopaminergic neurons based on a robust differentiation protocol involving the use of small molecules. For characterization, we collected samples at different timepoints during the differentiation procedure to assess gene and protein expression and compared these to commercially available induced pluripotent stem cell derived dopaminergic neurons (iCell DopaNeurons). As expected, expression of pluripotency markers NANOG, OCT4 and SOX2

was high at the pluripotency stage (day 0, D0) and immediately dropped in the first few days of the differentiation procedure. Early development of dopaminergic neurons was confirmed by detecting expression of Nestin, LMX1A, FOXA2, OTX2 and NURR1 from D16 onwards. Additionally, cells were predominantly neurons based on βIII-Tubulin expression. Expression of mature dopaminergic neuronal markers TH and EN1 was low expressed at day 20, when compared to the iCell Dopaneurons from Fuijifilm, suggesting the lack of fully mature dopaminergic neurons phenotype. Ongoing studies are focused on characterizing the functional phenotypes of the differentiated dopaminergic neurons and iCell DopaNeurons WT and PD GBA N370S, 11344 (mutant) using Microelectrode Arrays (MEA). Taken together, we successfully demonstrated that human embryonic stem cells be differentiated into early-stage dopaminergic neurons with the potential of further maturation. This *in vitro* model can be used in the discovery of novel targets and drugs for therapeutic intervention for Parkinson's disease.

Disclosures: M. Bsibsi: None. **M. Zanella:** None. **C. Gomez-Puerto:** None. **C. van den Berg:** None. **B. Gürkan:** None. **K. Lo:** None. **D. Ketskemety:** None. **S. Vermond:** None. **A.K. Chouhan:** None. **D. Magnani:** None. **C. Loomans:** None. **S. Kostense:** None. **M. Vlaming:** None. **D.F. Fischer:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.06/D16

Topic: C.03. Parkinson's Disease

Support: MJFF-17240
MJFF-020706
G031324N to W.V

Title: Identification and characterization of nanobodies which improve the stability and activity of glucocerebrosidase through a novel allosteric mechanism

Authors: *C. SINISGALLI[1], T. DAL MASO[2,3], G. ZILIO[4], S. BALLET[5], E. GREGGIO[6], W. VERSÉES[7,8], N. PLOTEGHER[6];
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Abstract: *GBA1* gene encodes the enzyme glucocerebrosidase (GCase) which catalyses the hydrolysis of glucosylceramide to glucose and ceramide within lysosomes. Mutations in *GBA1*

gene affect the activity, the correct folding and trafficking of the protein. Homozygous or compound heterozygous mutations cause the lysosomal storage disorder Gaucher disease, while heterozygous mutations are the most frequent genetic risk factor for Parkinson's disease (PD). Typically, these mutations impact on GCase stability, trafficking or activity. Different therapeutic approaches have been proposed targeting GCase, but for PD and especially for neuropathic forms of GD no cure is available. In the present study, we developed and characterized several nanobodies (Nbs) targeting and acting as chaperones for GCase using an allosteric mechanism that differs, to the best of our knowledge, from the mechanisms exploited by the currently available GCase chaperones. We identified a subset of Nbs that bind with nanomolar affinity to GCase (Kd = 2.3±0.7 nM). Based on an in vitro biochemical characterization, we grouped the Nbs in two classes: Nbs that improve the activity of the enzyme and Nbs that increase GCase stability *in vitro*. The most promising Nbs were selected, expressed in vector for expression in mammalian cells and tested in wild type HEK293T and CRISPR/Cas9 *Gba1* knock down cell models overexpressing the N370S mutant. The selected Nbs significantly improved GCase lysosomal activity in live cells, as evaluated by flow cytometry by using the 5-(pentafluorobenzoylamino) Fluorescein Di-β-D-Glucopyranoside (PFB-FDGlu), a specific lysosomal substrate. ENDO H and PNGase assay together with colocalization studies performed by confocal imaging demonstrated that a subset of Nbs can improve GCase trafficking by increasing the amount of the active protein in lysosomes. Interestingly, also the activity of N370S GCase, which is one of the most frequent GCase mutant, was improved by different Nbs, *in vitro* and in cell models. These results lay the foundation for the development of new therapeutics exploiting the identified Nbs to either stabilize or activate wild type and mutant GCase in PD and GD .

Disclosures: C. Sinisgalli: None. **T. Dal Maso:** None. **G. Zilio:** None. **S. Ballet:** None. **E. Greggio:** None. **W. Versées:** None. **N. Plotegher:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.07/D17

Topic: C.03. Parkinson's Disease

Support: NIH grants NS127391
NIH grants NS129188
Parkinson's Cell Therapy Research Fund at McLean Hospital and Massachusetts General Hospital
Masson Family Endowed Scholar in Neurosurgery

Title: Pre-clinical safety and efficacy of human induced pluripotent stem cell-derived products for autologous cell therapy in Parkinson's disease

Authors: J. JEON[1], Y. CHA[1], Z. SHRESTHA[1], H. L. RYU[1], Y. HONG[1], H. JANG[1], B. SONG[2], J. S. SCHWEITZER[2], T. HERRINGTON[3], P. LEBLANC[1], B. CARTER[2], *K. KIM[1,2]; [1]McLean Hospital/Harvard Med. Sch., Belmont, MA; [2]Neurosurg., [3]Neurol., Harvard Med. Sch., Boston, MA

Abstract: Human induced pluripotent stem cell (hiPSC)-derived midbrain dopamine cells (mDACs) hold promise as cell sources for autologous cell replacement therapy (CRT) in Parkinson's disease (PD). We previously documented the clinical implantation of patient-derived mDACs, differentiated *in vitro* from autologous hiPSCs, in a patient with idiopathic PD, demonstrating a proof-of-concept for autologous CRT in PD. However, before clinical implementation, establishing standardized regulatory criteria is imperative. Moreover, demonstrating that clinical-grade hiPSCs can be generated from diverse sporadic patients, regardless of their genetic backgrounds, is essential. Toward this end, we conducted a comprehensive assessment of multiple hiPSC lines derived from five sporadic PD patients to evaluate the safety and efficacy of mDACs derived from these lines. Initially, we utilized a single clinical-grade hiPSC line obtained from a patient's skin biopsy, along with another line derived from Coriell-banked fibroblasts. These hiPSC lines were differentiated into mDACs using our improved *in vitro* differentiation method and underwent thorough evaluation using a series of *in vitro* and *in vivo* assays, including a 39-week mouse Good Laboratory Practice (GLP) safety study focusing on tumorigenicity, toxicity, and biodistribution. Additionally, we generated multiple hiPSC lines from skin biopsies of three additional sporadic PD patients, identifying clinical-grade hiPSC lines and conducting non-GLP safety and efficacy studies. Furthermore, given the diversity among individuals in personalized cell therapy, we investigated whether these diverse genetic backgrounds affect reprogramming, *in vitro* differentiation, safety, and functional outcomes. Our results will be discussed in the context of autologous and other types of cell therapy, and a regulatory guideline will be proposed.

Disclosures: J. Jeon: None. **Y. Cha:** None. **Z. Shrestha:** None. **H.L. Ryu:** None. **Y. Hong:** None. **H. Jang:** None. **B. Song:** None. **J.S. Schweitzer:** None. **T. Herrington:** None. **P. Leblanc:** None. **B. Carter:** None. **K. Kim:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.08/D18

Topic: C.03. Parkinson’s Disease

Support: AcRF-MOE Tier 1 funding

Title: Theranostic potentials of nitrogen-doped graphene quantum dot nanoparticles targeting alpha-synuclein protein aggregation in Parkinson’s Disease

Authors: *M. PALANIVEL, K. GHOSH, P. PADMANABHAN, K.-L. LIM, B. GULYAS; Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore

Abstract: Parkinson's disease (PD) is debilitating neurodegenerative movement disorder, in which the aggregation of a physiological protein, alpha-synuclein (a-syn), into toxic fibrils, is widely theorized to cause the death of dopaminergic neurons, leading to motor dysfunction. In this study, we evaluated the theranostic potentials of nitrogen-doped graphene quantum dot (NGQD) nanoparticles against a-syn aggregation, as well as their biocompatibility through *in vitro* studies and biophysical assays. Three distinct types of nanoparticles, NGQD1, NGQD2, and CUR@NGQD, were synthesized, with potential for a-syn detection, inhibiting aggregation of a-syn, or both, respectively. Extensive spectrometric and imaging methods were used to thoroughly analyse the properties of NGQDs. The NGQDs were nanometre sized and exhibited UV-Visible and near infrared fluorescence emissions, indicating biocompatibility with cells and tissues, and their potential use as an optical probe for a-syn detection. It was verified, through fluorescence shift assays, that NGQD1 possessed diagnostic capabilities targeting a-syn detection. Meanwhile, NGQD2 exhibited promise in inhibiting aggregation of wild type a-syn, A53T and A30P variants. Aggregation kinetics assays demonstrated that even at a low concentration of 3.13µg/mL, NGQD2 achieved significant inhibition against wild type a-syn aggregation totalling approximately 72%. In addition, NGQD2 showed close to 100% and around 81% inhibition against A53T aggregation and against A30P aggregation respectively. CUR@NGQD was formulated by the conjugation of curcumin, a small molecule polyphenol well-known to possess anti-aggregative properties against a-syn, onto the surface of NGQD1. In addition to reducing aggregation of wild type and mutant a-syn variants, CUR@NGQD further demonstrated diagnostic potentials for a-syn through fluorescent titration with various protein concentrations. These demonstrated the theranostic potential of CUR@NGQD in both detecting a-syn and reducing its aggregation. Moreover, through *in vitro* cell viability assays with wild-type and A53T-transfected SH-SY5Y human neuroblastoma cell line, the NGQDs displayed very limited cytotoxicity to the cells. Confocal microscopy revealed significant temporal uptake of the NGQDs by SH-SY5Y cells. Our current experimental design includes investigating the theranostic potential against a-syn aggregation and detection *in vitro* through imaging, protein and gene expression, and *in silico* studies. This work paves the way for the development of theranostic NGQD nanoparticles that can both detect and inhibit a-syn aggregation.

Disclosures: M. Palanivel: None. **K. Ghosh:** None. **P. Padmanabhan:** None. **K. Lim:** None. **B. Gulyas:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.09/D19

Topic: C.03. Parkinson's Disease

Title: Preclinical validation of HDAC6 as a disease-modifying therapeutic target for Parkinson's Disease

Authors: *R. E. JAMES, F. A. SCHROEDER, L. EVANS, T. GILBERT;
Eikonizo Therapeutics, Inc., Cambridge, MA

Abstract: In Parkinson's disease (PD), dopaminergic neurons (DANs) of the nigrostriatal system progressively degenerate, leading to motor and non-motor cognitive, behavioral, and emotive dysfunction. PD is the second most common and fastest growing neurodegenerative disease, but there are no disease-modifying therapeutics. Several processes contribute to DAN loss in PD, including altered alpha-synuclein (αSyn) proteostasis leading to αSyn accumulation in Lewy bodies (LBs), mitochondrial dysfunction and oxidative stress, dysregulated mitochondrial quality control, defective axonal transport, and neuroinflammation. Given the multiple etiologies contributing to DAN loss, is it possible to address these disrupted cellular pathways with a single therapeutic target? The enzyme histone deacetylase 6 (HDAC6) impacts each of these pathways. Unlike nuclear HDACs, HDAC6 deacetylates only cytoplasmic substrates due to its restricted cytoplasmic localization. Acetylation of alpha-tubulin and tau, two key HDAC6 substrates, is significantly decreased in Braak stage IV-VI PD brain tissues and a catalytically active form of phosphorylated HDAC6 accumulates in LBs. Together, these pathological findings implicate excessive HDAC6 catalytic activity in PD. Consistently, various first-generation tool HDAC6 inhibitors have shown benefit for HDAC6 inhibition (HDAC6i) in mitochondrial neurotoxin (e.g., 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]) induced PD models. Yet development of an HDAC6 inhibitor therapeutic has been hindered by a lack of brain-penetrant compounds with suitable drug-like properties. We have overcome this challenge by developing orally bioavailable next-generation small molecule HDAC6 inhibitors that are CNS-penetrant (K_{puu}, brain >0.5), potent (IC_{50} <100 nM), and highly selective against all HDAC paralogs (>1000-fold). We demonstrate here using both αSyn preformed fibril-induced injury and MPTP PD models that our next-generation HDAC6 inhibitors enhance αSyn clearance and reduce mitochondrial reactive oxygen species in DANs, and diminish reactive microgliosis, culminating in improved neuronal health and DAN survival. These results support the hypothesis that select inhibition of HDAC6 catalytic activity confers a multifaceted advantage in treatment of PD by 1) restoring αSyn proteostasis; 2) reducing oxidative stress; and 3) dampening neuroinflammatory responses. These findings substantiate the potential broad applicability of HDAC6i in PD, regardless of familial or idiopathic etiology, and position HDAC6i as a viable therapeutic target to repair multiple damaged cellular pathways in PD.

Disclosures: R.E. James: A. Employment/Salary (full or part-time):; Eikonizo Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eikonizo Therapeutics, Inc. **F.A. Schroeder:** A. Employment/Salary (full or part-time):; Eikonizo Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eikonizo Therapeutics, Inc. **L. Evans:** A. Employment/Salary (full or part-time):; Eikonizo Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eikonizo Therapeutics, Inc. **T. Gilbert:** A. Employment/Salary (full or part-time):; Eikonizo Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty,

receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eikonizo Therapeutics, Inc..

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.10/D20

Topic: C.03. Parkinson's Disease

Support: NIH R01-NS117757 (D.K.C.)
NIH R01-NS127895 (D.K.C)

Title: Human Tissue-Engineered Nigrostriatal Pathway to Reconstruct Dopaminergic Axon Tract for Treating Parkinson's Disease

Authors: *D. CHOUHAN[1,2,4], K. D. BROWNE[2,4], W. J. GORDIAN VELEZ[3,4], S. KARANDIKAR[3,4], K. YANKSON[3,4], D. CULLEN[2,3,4];
[2]Dept. of Neurosurg., [3]Dept. of Bioengineering, [1]Univ. of Pennsylvania, Philadelphia, PA; [4]Ctr. for Neurotrauma, Neurodegeneration, & Restoration, Corporal Michael J. Crescenz Veterans Affairs Med. Ctr., Philadelphia, PA

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. The motor symptoms of PD result from the death of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and their axonal projections comprising the nigrostriatal pathway (NSP), which ultimately leads to the loss of dopamine in the striatum. Ectopic implantation of DA neurons in the striatum has shown promise in restoring dopamine levels; however, this approach does not consider the importance of the SNpc-striatal feedback loop intrinsic in the NSP. To address this shortcoming, we sought to reconstruct the entire fiber tract by engineering a NSP comprised of prefabricated DA neuronal aggregates and their associated long-distance axon bundles within a hydrogel encasement. By manipulating cell density and the dimensions of the scaffold, we have developed multiple variations of tissue-engineered nigrostriatal pathways (TE-NSPs) using human induced pluripotent stem cell (iPSC)-derived DA neurons with axonal tracts ranging from 5mm to 25mm in length. The TE-NSPs fully grew long-distance axons by 21-28 days, and exhibited a discrete population of DA neurons projecting tyrosine hydroxylase (TH+) axon tracts. When implanted in a rat PD model, small-scale TE-NSPs (345/160 µm outer/inner diameter, 6 mm long, 15,000 cells) demonstrated circuit reconstruction *in vivo* with anatomical fidelity. Further, to mimic the nigrostriatal pathway of the human brain, we designed human-scale TE-NSPs by seeding 220,000 DA neurons in a large-scale scaffold (973/500 µm outer/inner diameter). This human-scale microtissue displayed 2.5cm long DA axonal tracts and exhibited survival up to 6 months *in vitro* with robust TH+ axonal tracts and 90% cell viability. To further target clinical translation, we have also established methodologies to biopreserve the TE-NSPs under hypothermic conditions for efficient transportation and validated their optimal viability and long-term survivability. TE-NSPs have

promise as a tissue engineered medical product to reconstruct the lost neuroanatomical circuitry associated with PD.

Disclosures: D. Chouhan: None. **K.D. Browne:** None. **W.J. Gordian Velez:** None. **S. Karandikar:** None. **K. Yankson:** None. **D. Cullen:** Other; D.K.C. is a scientific co-founder of Innervace Inc., a University of Pennsylvania spin-out company focused on translation of advanced regenerative therapies to treat central nervous system disorders..

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.11/D21

Topic: C.03. Parkinson's Disease

Support: 5T32NS121780-03

Title: Activation of astrocytes by pathogenic alpha-synuclein

Authors: *M. NELSON[1], S. DEOL[2], K. A. MAGUIRE-ZEISS[3];
[1]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [2]Georgetown Univ., Washington DC, DC; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: ***Activation of astrocytes by pathogenic alpha-synuclein***[1,2]Nelson, M, [2]Deol, S, [1,2,3]Maguire-Zeiss, K[1]Interdisciplinary Program in Neuroscience, [2]Department of Neuroscience & [3]Biology,Georgetown University, Washington DC
Disclosures: Matthew Nelson: None. Dr. Maguire-Zeiss: None. Sunain Deol: None.
Abstract: During Parkinson's Disease, alpha-synuclein (α-syn) fibrils aggregate to form intracellular deposits called Lewy bodies and Lewy neurites, these fibrils can be released from neurons into the extracellular space. Mouse cortical microglia exposed to α-syn aggregates demonstrate increased production of the pro-inflammatory cytokines. Less is known about the effects of α-syn on astrocyte activation, microglia and astrocyte cross talk, and how microglia modulate astrocyte activation. Here we investigate the role of microglia-derived exosomes on astrocyte reactivity following exposure to α-syn. Primary cortical mouse glial cells from p0-p3 c57 wild type mice were grown for 12-24 days at 37ºC prior to treatment. Primary microglia were plated 24 hours prior to treatment with the anti-inflammatory drug, resveratrol (50uM) or vehicle, cell media was collected, and extracellular vesicles (EVs) were extracted and characterized. Astrocytes were treated simultaneously with α-syn or vehicle and the various microglia-derived EVs for 24 hours. Enriched astrocytes (n=3) exposed to α-syn (1ug/ml) for 24hours showed significant increases in mRNA expression for inflammatory cytokines (analysis via Student-t test and ANOVA) IL-6 (<0.001), Iba-1 (0.0013), TNF-α (0.0001), CCL2 (0.0008),NLRP3 (0.0084), caspase-1 (0.0087) and IL-1β (0.0018) as well as TNF-α release (<0.0001). Enriched astrocytes (n=3) treated with microglia-derived resveratrol EVs and α-syn

showed significant decreases in IL-6 (0.0006), IL-1β (<0.0001), and CCL2 production (<0.0001)compared to α-syn-exposed astrocytes incubated with microglia-derived vehicle EVs. These data support the hypothesis that α-syn triggers a significant inflammatory response in astrocytes, and that EVs derived from resveratrol-treated microglia attenuate this activation pathway in astrocytes. We propose to next investigate the microglia EV content and to pursue the use of EVs as a therapeutic approach in aging and neurodegeneration models.

Disclosures: M. Nelson: None. **S. Deol:** None. **K.A. Maguire-Zeiss:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.12/D22

Topic: C.03. Parkinson's Disease

Title: Investigating the Molecular Mechanisms of Adipose Stem Cell-Derived Exosomes for Preventing Neurodegeneration in an a-Synuclein Model of Parkinson's Disease

Authors: *C. LOGAN[1], S. ABDELMABOUD[1], C. E. HUDSON[2], N. A. PATEL[3], K. R. NASH[4], P. C. BICKFORD[5];
[1]Univ. of South Florida, Tampa, FL; [2]James A. Haley VA Med. Ctr., Tampa, FL; [3]JAH VA and Univ. of South Florida, Tampa, FL; [4]Mol. Pharmacol. and Physiol., Univ. of South Florida, Tampa, FL; [5]Neurosurg. and Brain Repair, Univ. of South Florida, Tampa, FL

Abstract: Parkinson's Disease (PD) is the second most prevalent neurodegenerative disease with over 90,000 people diagnosed each year. Treatment options are limited but include medications, surgery, and lifestyle changes. Previous research has shown that exosomes can migrate to injury sites to slow down the progression of a disease or injury. Our goal is to use exosomes derived from human adipose stem cells (hASC) to treat PD. To model PD, we injected recombinant adeno-associated virus (rAAV) expressing a-synuclein (Syn) into the substantia nigra (SN) of male Fisher rats. Unilateral injection into the SN of rat's results in progressive loss of DA neurons and development of paw bias on the contralateral side to injection. We tested the rats for paw bias at baseline, then divided animals into groups to receive 2 mL of either rAAV9-Syn or the control vector rAAV9-mKate (0.5 x 1013 vector genomes/mL). Three weeks post-injection animals were split to receive intranasal administration of either: 100ug hASC exosomes (EXO) or PBS (control). After two months rats were euthanized and immunohistochemistry (IHC) was conducted to determine the extent of TH+ cell loss in the SN, and we conducted single cell RNA sequencing (scRNA seq) of the SN to observe any transcriptional changes. Using IHC, we found injection of Syn lead to decreased TH+ cells and increased levels of MHCII+. Treatment with 100ug of exosomes prevented loss of TH+ cells and MHCII+ was no longer increased from control in the SN. For scRNA seq, we observed distinct subclusters in both Syn+PBS and Syn+EXO treated animals. We found SYN+PBS animals had markers involved in activation of the innate immune response and neuroinflammation with elevated levels of IL1b. In exosome

treated animals, we observed increased immune regulation via FKBP5 and CSF1R in our microglia cluster. Furthermore, we found markers involving antigen presentation, apoptotic signaling, and notch signaling in treated animals. Based on our results, in the SN, exosomes may be involved in reducing microglia activation and play a role in regulating T cell activation. We plan to continue researching the interactions between microglia and exosomes, as well as the interactions between exosomes and the immune system.

Disclosures: C. Logan: None. **S. Abdelmaboud:** None. **C.E. Hudson:** None. **N.A. Patel:** None. **K.R. Nash:** None. **P.C. Bickford:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.13/D23

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

Title: Study of the protective effect of Corydalis sibirica extract in vitro

Authors: *A. JALSRAI, Senior[1], *A. JALSRAI, Senior[2];
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Abstract: Study of the protective effect of *Corydalis sibirica* extract in vitro
Jalsrai A[1], Myadagbadam U[1]., Anu A[1]., Cong Y[3]., Hseih-Li H.M[4]
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Background: *Corydalis sibirica* is a member of the Papaveraceae family. Certain species of *Corydalis*, such as *Corydalis turtchaninovii*, *Corydalis decumbens*, and *Corydalis incisa*, exert an analgesic action and exhibit antihypertensive, antirheumatic properties. The major ones are d-corydaline, dl-tetrahydropalmatine and corydalis H, I, J, K and L. The pharmacological effects of *Corydalis sibirica* have not been thoroughly studied. In this study, we examined the effects of the *Corydalis sibirica* extract using various in vitro models.**Methods:** The aerial part of *Corydalis sibirica* was collected from Tuv aimag in Mongolia and preserved in 70% ethanol. The specimen was filtered and vacuum-dried to prepare the extract for use in the study. Hydroxyl radicals were detected using spin trapping agents with ESR spectroscopy. The protective effects of the extract were assessed using in vitro insult assays, i.e. malondialdehyde (MDA 100μM)-induced mitochondrial dysfunction and H_2O_2-induced cortical neuron toxicity. **Results:** The *Corydalis sibirica* extract showed a weak scavenging effect on hydroxyl radicals with IC_{50} of 19.46 mg/ml. We examined the effect of the *Corydalis sibirica* extract on cultured cortical neurons under oxidative stress and found that pretreatment with the extract significantly inhibited H_2O_2-induced cell death in cortical neurons. Additionally, the ethanolic extract of *Corydalis*

sibirica showed a significant decrease in oxidative damage caused by malondialdehyde enhancing the activity of mitochondrial respiratory transport chains (complex I and complex II) at a concentration 32 mg/ml in isolated brain mitochondria. **Conclusion:** These results suggest that *Corydalis sibirica* may protect cells against oxidative damage.

Disclosures: A. Jalsrai: None. **A. Jalsrai:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.14/D24

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

Support: NIH Grant AG076917
NIH Grant AG049479
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NIH Grant TR002548
NIH Grant NS083498
NIH Grant AG072959
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NIH Grant AG063362

Title: Calpain-dependent cleavage products of DLP1 contributes to mitochondrial dysfunction and neurodegeneration in Alzheimer's disease through interacting with MAVS

Authors: *C. SHAO[1], W. WANG[2], X. ZHU[2];
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Abstract: DLP1, the key mitochondrial fission GTPase, is cleaved by calpain to produce a N-terminal fragment of DLP1. The levels of 55kDa DLP1 cleavage products were increased in the brain of AD patients. However, the pathophysiological function of the DLP1 cleavage products remains unknown. We first identified calpain cleavage by bioinformatic analysis, which was confirmed by mutagenesis studies. Synthesized peptides targeting the DLP1 cleavage site effectively blocked glutamate-induced calpain cleavage of DLP1 in rat primary neurons. Interestingly, overexpression of DLP1 cleavage products caused abnormal mitochondrial distribution, mitochondrial dysfunction, and increased cell death both in neuronal cell lines and rat primary neurons. Biochemical analysis revealed that DLP1 cleavage products are enriched in mitochondria and prone to form insoluble aggregates in mitochondria that likely affect mitochondrial signaling/function. Furthermore, DLP1 cleavage products have a stronger interaction with MAVS and activate the RLR inflammation pathway to induce cell apoptosis. Our study suggests that the increase in calpain-dependent DLP1 cleavage products in AD

contributes to mitochondrial dysfunction, neuroinflammation, and neuronal death. <!--EndFragment-->

Disclosures: C. Shao: None. **W. Wang:** None. **X. Zhu:** None.

Poster

PSTR453: Proteinopathies: Therapeutic Strategies: Cellular Models

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR453.15/D25

Topic: A.03. Stem Cells and Reprogramming

Support: NEI Grant R01EY033022
NEI Grant U24EY033269
BrightFocus Foundation Grant G2020369S
Gilbert Family Foundation Grant 923016

Title: A tri-culture system to explore the role of neuroinflammation in the degeneration of retinal ganglion cells

Authors: J. HARKIN, C. GOMES, ***J. MEYER**;
Stark Neurosciences Res. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Glaucoma is the leading cause of irreversible blindness worldwide, affecting approximately 80 million people. In animal models of glaucoma, microglial activation has been associated with changes in morphology and proliferation, as well as the release of inflammatory factors, which contribute to the neurodegeneration of retinal ganglion cells (RGCs). Due to major differences identified between rodent microglia and RGCs compared to humans, there is a critical need for the development of novel human models that can be used to explore the cellular crosstalk between human microglia and RGCs and the role of these interactions in diseases such as glaucoma. In the current study, we differentiated both microglia-like cells (MGLs), RGCs and astrocytes from human induced pluripotent stem cells (iPSCs). Microglial activation was then induced using Lipopolysaccharide (LPS) and confirmed using morphological analyses, immunostaining, and cytokine/chemokine profile screening. Healthy and LPS-activated microglia were then co-cultured with RGCs for up to 3 weeks and the effects of microglia upon RGCs were assessed using measurements of neurite complexity and functionally via multielectrode array. Finally, healthy and LPS-activated microglia and RGC co-cultures were also grown with astrocytes to assess both direct and indirect effects of activated microglia upon RGCs. Results indicated that following activation via treatment with LPS, MGLs exhibit more amoeboid morphological features and increased the expression of MHC-II, characteristic of activated microglia. MGLs also released significantly elevated levels of inflammatory cytokines including IL-6, IL-8, IL-1B and TNFa. When co-cultured with astrocytes, LPS-activated microglia promoted astrocyte reactivity. Additionally, co-cultures of MGLs and RGCs revealed that activated MGLs reduced RGC neurite complexity and decreased neuronal excitability,

suggesting a contribution of microglia activation to RGC neurodegeneration. Finally, combined cultures of MGLs, astrocytes, and RGCs demonstrated complex interactions between cell types. Taken together, the current study establishes the first known study to develop a human cellular model that allows for the examination of cellular interactions between human microglia, astrocytes and RGCs, including the study of microglial contributions to RGC neurodegeneration and neuroinflammation.

Disclosures: J. Harkin: None. **C. Gomes:** None. **J. Meyer:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.01/D26

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

Support: NIH Grant 2RO1NS086778-10A1 Awarded to SVT

Title: A focused study to find regulators of DRPLA toxicity in Drosophila

Authors: *T. KULA[1], M. V. PRIFTI[1], R. DULAY[1], N. C. PATEL[1], K. RICHARDSON[1], S. V. TODI[1,2];
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Abstract: One member of the family of the polyglutamine diseases of the nervous system, which comprises nine members, is Dentatorubral-pallidoluysian Atrophy (DRPLA). DRPLA is a rare autosomal disease for which there is no therapeutic option in the clinic. We recently generated novel models of DRPLA in *Drosophila melanogaster*, with the purpose of understanding the biology of this disease and to find potential therapeutic entry points. Here, we describe an ongoing effort in the laboratory to find genes that regulate DRPLA toxicity in the fruit fly. We use a quantifiable system that relies on CD8-tagged GFP to report overall tissue health alongside expression of the DRPLA protein, Atrophin-1. We will report our findings from this limited study that focuses on various protein quality control genes and also genes related to the immune pathway.

Disclosures: T. Kula: None. **M.V. Prifti:** None. **R. Dulay:** None. **N.C. Patel:** None. **K. Richardson:** None. **S.V. Todi:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.02/D27

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

Support: Deans Diversity Fellowship, Wayne State University Graduate School, Awarded to Matthew Prifti
NIH Grant 2R01NS086778-10A1 Awarded to Sokol Todi

Title: Insights into Dentatorubral-Pallidoluysian Atrophy from a new Drosophila model of disease

Authors: *M. V. PRIFTI[1], N. C. PATEL[1], R. DULAY[2], T. KULA[1], W.-L. TSOU[1], K. RICHARDSON[1], S. V. TODI[1,3];
[1]Pharmacol., Wayne State Univ., Detroit, MI; [2]Pharmacol., Wayne State Univ., Shelby Township, MI; [3]Neurology, Wayne State University, Detroit, MI

Abstract: Dentatorubral-pallidoluysian Atrophy (DRPLA) is a rare, autosomal dominant, neurodegenerative disorder which manifests symptoms of ataxia, dementia and epilepsy with varying degrees of severity depending on age of onset. DRPLA, a member of the polyglutamine (polyQ) family of diseases, is characterized by an abnormal repeat expansion of CAG triplet report in protein-coding region of the gene ATN1. The resulting protein, Atrophin-1 functions in part as a transcriptional co-repressor. Similarly to other polyQ diseases, when the polyQ of ATN1 is expanded to a pathogenic length of 48 to 93, it forms aggregates which may in part contribute to overall neuronal toxicity and cell death. We recently generated transgenic Drosophila melanogaster lines that express full-length, human ATN1 with a normal (Q7) or pathogenic (Q88) repeat. We find that expression of both wild-type and pathogenic ATN1 is toxic in the fly with varying severity, depending on the tissue where it is expressed; the pathogenic form its consistently more toxic than the wild-type version. Additional studies highlight various members of the protein quality control pathway and immune pathway as important regulators of the toxicity of ATN1 in flies in a manner that does not always correlate with protein levels. Collectively, our data indicate key factors as potential targets for therapeutic development for DRPLA.

Disclosures: M.V. Prifti: None. **N.C. Patel:** None. **R. Dulay:** None. **T. Kula:** None. **W. Tsou:** None. **K. Richardson:** None. **S.V. Todi:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.03/Web Only

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

Support: KAKENHI JP 23K06976

Title: The enhancement of protein quality control system in models of neurodegenerative diseases

Authors: *H. ADACHI[1], Z. HUANG[1], T. TOYOTA[1], Q. QIANG[2], E. BAT-ERDENE[1], T. SATO[3], S. TSUJI[4];
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Abstract: Polyglutamine (polyQ) diseases are inherited neurodegenerative diseases caused by the expansion of a polyQ tract within the causative genes. In chronic neurodegenerative disorders such as polyQ diseases, commonly observed phenotypes include the abnormal accumulation of disease-causing proteins and the formation of nuclear and cytoplasmic inclusions. Hikeshi is essential for the entry of the Hsc70/Hsp70 (Hsp70s) to the nucleus under stress condition. Hsp70s are rapidly and transiently relocated from the cytoplasm into the nucleus and nucleolus in response to heat shock. Inside the nucleus, Hsp70s dissociate from Hikeshi and bind native or non-native client proteins and function as a molecular chaperone, likely reversing and attenuating the multiple heat shock-induced nuclear phenotypes and therefore protecting the cells from heat shock damage. Homozygous missense mutations in the human Hikeshi gene cause congenital leukodystrophy associated with early onset spastic paraparesis, acquired microcephaly and optic atrophy.We examined the effects of the overexpression of Hikeshi in cultured cell models of neurodegenerative diseases. Neuronal cells were transfected using Lipofectamine 2000 with plasmids encoding mutant androgen receptor (AR), atrophin-1, huntingtin, ataxin-1, ataxin-3, transcription factor EB (TFEB), and Hikeshi. We generated transgenic mice expressing full-length human Hikeshi under the control of a cytomegalovirus enhancer and a chicken ß-actin promoter, and crossed the dentatorubural-pallidoluysian atrophy (DRPLA) mice (Q113) with mice overexpressing human Hikeshi.The overexpression of Hikeshi decreased the expression of each causative protein in the neuronal cell models. On the other hand, reduction of Hikeshi increased the expression levels of mutant proteins. TFEB enhances reduction in mutant proteins with HIKESHI. Unfortunately, the overexpression of Hikeshi did not demonstrate any behavioral changes in the mouse model of DRPLA (n=20) compared with wild-type littermates (n=20).These findings demonstrated that the high expression of Hikeshi enhanced the degradation of the disease-causative proteins, and promoted therapeutic effects in cellular models. The precise mechanism utilized by the mutant proteins needs to be determined in future studies The precise mechanism of removal and/or refolding of the mutant proteins in which protein quality control systems function appropriately, needs to be determined in future studies.

Disclosures: H. Adachi: None. **Z. Huang:** None. **T. Toyota:** None. **Q. Qiang:** None. **E. Bat-Erdene:** None. **T. Sato:** None. **S. Tsuji:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.04/D28

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

Support: NINDS Grant NS132097

Title: A vault bionanoparticle-encapsulated Frataxin gene-targeted histone demethylation for contracting GAA repeats in Friedreich's Ataxia

Authors: *R. C. ARMBRISTER[1], C.-Y. LAI[2], Y. LAI[3], Y. LIU[4];
[2]Mechanical and Materials Engin., [3]Envrn. Hlth. Sci., [4]Arts and Sci., [1]Florida Intl. Univ., Miami, FL

Abstract: Friedreich's Ataxia (FRDA), the most prevalent form of recessive ataxia caused by the expansion of GAA repeats in the first intron of the frataxin (FXN) gene, leading to FXN gene silencing. No effective treatments for FRDA are available. Our previous studies have unveiled that temozolomide (TMZ) that can induce alkylated DNA bases and are predominantly repaired by the DNA base excision repair (BER) preferentially causes contractions of GAA repeats at the FXN gene in FRDA patient lymphoblasts and transgenic mouse cerebellar neural cells. We further revealed significant inhibition of H3K9 methylation (H3K9me) by TMZ, leading to decreased H3K9 trimethylation (H3K9me3) and increased H3K9 acetylation (H3K9ac) on the expanded GAA repeats in FRDA neural cells. This spurred the development of a bioengineered major vault protein (MVP) system encapsulating the FXN gene-targeted CRISPR/dCas9-KDM4D sgRNA-protein complex. This innovative approach facilitates the direct delivery of histone demethylase to the FXN gene, inducing demethylation of H3K9me2/3 and BER-mediated GAA repeat contraction. Given the natural occurrence of vaults in the central nervous system, our engineered MVP protein nanoparticles hold promise for traversing the blood-brain barrier, delivering specific proteins in a gene-targeted manner. Our study will uncover a novel paradigm, elucidating the synergistic interplay between CRISPR/dCas9-mediated FXN gene-targeted histone demethylation and DNA repair in mediating GAA repeat contraction in FRDA. This pioneering work will introduce the first human natural nanoparticle, vault-mediated FXN gene-targeted platform to disrupt heterochromatin and induce DNA repair-mediated contraction of expanded GAA repeats in FRDA, heralding a new era in FRDA treatment.

Disclosures: R.C. Armbrister: None. **C. Lai:** None. **Y. Lai:** None. **Y. Liu:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.05/D29

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

Support: Indian Council of Medical Research; Grant ID: BMI/11(19)/2022)

Title: Variations in the FXN gene's regulatory regions to understand the transcriptional barriers in Friedreich's Ataxia: an in silico analysis

Authors: *V. KUMAR[1], V. SWARUP[2], A. AHUJA[1], D. DEEPIKA[2], A. SRIVASTAVA[2]; [1]Dept. of Neurol., All India Inst. of Med. Sci., New Delhi, India; [2]Dept. of Neurol., All India Inst. of Med. Sci., New delhi, India

Abstract: Background: Friedreich's ataxia (FRDA) is one the most common, autosomal recessive disorder in Indian subcontinent, Europe, Middle East and North Africa. Clinical characters like neurodegeneration within the cerebellum and spinal cord, hypertrophic cardiomyopathy, and predisposition to diabetes can observed in patient suffering from FRDA. This disease is caused by very low expression of frataxin protein in patients. The causative *frataxin* (*FXN*) gene lies on chromosome 9 (69035751-69079076). Several pathogenic mechanisms have been reported like abnormal biallelic expansion of GAA repeats in intron-1 of *FXN* gene, RNA-DNA hybrid, DNA triplex, heterochromatin formation and mutations in its exons. *FXN* gene has minimal promoter and its regulatory regions spans approximately 107300 nucleotides upstream and also include intron-1. Heterochromatin formation has been reported in these regulatory regions. However, any genetic variations have not yet been reported in these regions. The aim of the present study was to identify and annotate genetic variation in these regions.
Methodology: The coordinates of 9 regulatory regions were obtained from Ivan et al., 2020 (PMID: 32408537). The coordinates of theses regulatory region were updated from hg37 to hg38 using lift genome annotation of UCSC genome browser. These regulatory regions were investigated for any possible variations using Ensembl database. **Observations:** Total 53 variations were identified in 9 regulatory region. Region 5 and 6 have lowest (2) variations while region 8 has highest number (14) of variations. Four variations with clinically significance in FRDA have been found in region 3, of which two are labelled as pathogenic. No other region was found the clinically significant variations.
Conclusion: These regulatory regions contain numerous variations. However only two variations have been reported as pathogenic in the database. The current study is in silico analysis only. Further validation of these variations in patient sample is necessary to divulge their role in *FXN* expression in patients.

Particulars of variations in region 3 are:

S. No.	Variation ID	Clinical Significance	Coordinate(s)	Alleles	ClinVar ID	Consequence
1.	rs141935559	Pathogenic	9:69035936-69035939	CCCC/CC C/CCCCC	RCV001092266.7	Frameshift variant
2.	rs104894108	Pathogenic	9:69035785	G/A/T	RCV001579769.4	Start lost
3.	rs2481598	Benign	9:69035836	A/G/T	RCV000676782.9	Synonymous variant
4.	rs995690945	Uncertain significance	9:69035928	C/A/G	RCV001334263.1	Missense variant

Disclosures: V. Kumar: None. **V. Swarup:** None. **A. Ahuja:** None. **D. Deepika:** None. **A. Srivastava:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.06/D30

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

Support: CCCRP Award No. CO210066

Title: Characterization of dystonia following novel combined craniectomy and telemetry device implantation surgery in mice.

Authors: *J. A. LEIGHTON[1], E. A. JOHNSON[2], M. ELLIS[2], A. METHVIN[2], J. JANSSEN[2]; [1]USAMRICD, Aberdeen Proving Ground, MD; [2]Neurosci., USAMRICD, Aberdeen Proving Ground, MD

Abstract: Rodent surgical procedures are a valuable aspect of experimental research as they allow for models and metrics to be tailored to meet specific study goals. Two common rodent surgical procedures include craniectomy trephination and telemetry device implantation. Craniectomy procedures allow for easy access to the brain for experimental traumatic brain injury (TBI) and for the creation of cranial windows necessary for *in vivo* imaging of the brain. Meanwhile, telemetry device implantation allows for live electroencephalographic (EEG) recording to take place, a vital measure in studies concerning central nervous system activity. Our team's research is primarily concerned with the physiological effects of controlled cortical impact TBI and neurotoxic chemical insult in mice, leading us to develop a combined craniectomy and telemetry device implantation surgery that allowed for access to the brain and live EEG recording during experimentation. While most mice recovered normally within 72hrs of the procedure, we found that a small proportion of mice presented with post-operative dystonia. Aspects of the dystonia varied between individuals but almost always appeared as persistent twitch-like or twisting movements within 24hrs of surgery. The effects of this dystonia were related to half of all post-operative mortalities. For surviving mice, post-operative bodyweight recovery and return to normal locomotion and behavior were impeded even when dystonic movements resolved. Further, mice presenting with post-operative dystonia showed deficits in nesting, burrowing, and open field testing two weeks later even when bodyweight, mentation, and passively observed movement were otherwise normal. We suspect that the craniectomy portion of the surgery was the driving factor in development of dystonia given that our findings are consistent with literature describing damage to the cortex and lasting behavioral changes following craniectomy trephination. In sum, our combined craniectomy and telemetry device implantation surgery was largely successful. However, understanding the causes and broader consequences of dystonia in the small number of affected mice may reduce the need for early euthanasia and reduce variability in experimental results moving forward. Our recommendation is that animals undergoing this procedure or similar should be carefully evaluated for post-operative dystonia and later inclusion in experimental behavioral metrics.

Disclosures: J.A. Leighton: None. **E.A. Johnson:** None. **M. Ellis:** None. **A. Methvin:** None. **J. Janssen:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.07/D31

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

Title: Intracerebral multi-electrode local field potential recording in humans undergoing general anesthesia induction and emergence

Authors: *J. NATARAJ[1], *J. NATARAJ[2], M. S. BREAULT[3], A. SEYYED MOUSAVI[4], J. OLAYA[5], M. LIKER[6], E. N. BROWN[8], T. D. SANGER[7];
[1]EECS, Univ. of California, Irvine, Irvine, CA; [2]Univ. of California, Irvine, Sherman Oaks, CA; [3]The Picower Inst. for Learning and Memory, MIT, Brookline, MA; [4]Univ. of California Irvine, Irvine, CA; [5]Neurosurg., [6]Div. of Neurosurg., [7]Res., Children's Hosp. of Orange County, Orange, CA; [8]Brain and Cognitive Sci., MIT/Mass Gen. Hospital/Harvard Med. Sch., Cambridge, MA

Abstract: General Anesthesia (GA) is a reversible drug-mediated condition comprised of unconsciousness, amnesia, antinociception, and immobility with maintenance of physiological stability during a surgical procedure. Much has been learned recently about how anesthetics change brain dynamics to produce altered states of arousal like unconsciousness. Electroencephalography (EEG) studies show that dynamics change with drug dose and class, patient age, and patient state of health. However, opportunities to directly observe effects of anesthetics on human deep brain structures are sparse. We observed subcortical dynamics under the GABAergic anesthetics propofol and sevoflurane in three pediatric dystonia subjects who underwent placement of stereoelectroencephalography (sEEG) electrodes for staged deep brain stimulation. Recordings were obtained at two time points: emergence following sEEG implantation and induction during sEEG explantation one week later. We recorded frontal surface EEGs and local field potentials (LFPs) from the brainstem and thalamus: pedunculopontine nucleus (PPN), substantia nigra pars reticulata (SNr), ventral intermediate nucleus (VIM), ventralis oralis anterior and posterior nuclei (Voa/Vop), and ventral anterior nucleus (VA). We performed multitaper spectral analysis of data recorded during induction (awake baseline, post-propofol bolus, and post-propofol bolus with sevoflurane) and emergence (sevoflurane, and post-recovery of consciousness). We studied the dynamics mediated by propofol and sevoflurane in these normally inaccessible brain regions. The EEG of propofol and sevoflurane GA represents global neural activity, characterized by the presence of alpha (8-12 Hz) and slow-delta (0.1-3 Hz) oscillations. Sevoflurane can exhibit a theta rhythm (4-8 Hz). Exploratory analysis revealed that the observed subcortical regions show slow wave oscillations under propofol and sevoflurane mediated unconsciousness, maximally in the brainstem. Alpha oscillations were also present in all subcortical regions, maximally in the thalamus and on EEG. This distribution of oscillations is consistent with previously reported EEG, LFP, and neural spiking activity recorded in adult epilepsy patients. They also agree with computational models of the actions of GABAergic agonists in the thalamus and cortex. Our results illustrate the likely dynamics generated in brainstem and thalamus to create anesthesia-mediated unconsciousness.

To our knowledge this work represents the first reported pediatric recordings of subcortical brain regions and the first human recordings of brainstem regions during the anesthetic state.

Disclosures: J. Nataraj: None. **J. Nataraj:** None. **M.S. Breault:** None. **A. Seyyed Mousavi:** None. **J. Olaya:** None. **M. Liker:** None. **E.N. Brown:** None. **T.D. Sanger:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.08/D32

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

Support: NINDS and NIMH T32NS115705
Child Neurology CNCDP-K12
PERF Shields Grant GR533062
AAN Clinical Research Training Scholarship FP00001989

Title: Early sensorimotor cortical oscillatory changes in response to initiation of pallidal DBS

Authors: *A. ALPERS[1], N. ABDALLAH[2], K. LIZARRAGA[3], M. GOMEZ-RAMIREZ[4], A. L. HEWITT[5];
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Abstract: Deep brain stimulation (DBS) is an effective treatment for the motor symptoms of dystonia, Parkinson's disease (PD), and essential tremor. However it is not fully understood how DBS alters the brain networks involved. One target of DBS that provides therapeutic benefits in both dystonia and PD is the globus pallidus pars internas (GPi). A few prior studies show that low frequency (4-12 Hz) activity over sensorimotor cortex is higher in generalized dystonia than in healthy controls, and theta activity (4-7 Hz) positively correlates with dystonia severity scores. It takes weeks to months for dystonia symptoms to respond to DBS, but cortical oscillations have not been studied during this early period. To evaluate early effects of DBS on the sensorimotor network, we recorded local field potentials (LFPs) using high-density electroencephalography (EEG; 128 channels) and GPi DBS electrodes from n=13 subjects: 1) seven participants (4F, 65 ± 9 years) with dystonia secondary to PD who were implanted with DBS electrodes during the course of the study, 2) three participants (52 ± 16 years) with idiopathic generalized dystonia or dystonia secondary to cerebral palsy with chronic DBS, and 3) three controls (3F, 29 ± 14 years) with no movement disorder. During 1 minute EEG and GPi LFP recordings, participants rested in a chair with no DBS therapy. Data from each research visit was filtered (0.5 Hz highpass, 60 Hz notch). A fast fourier transform was used in 1 second time bins to calculate power spectral density (PSD) curves for data from each research visit. Total area under the PSD curve (AUC) was calculated for each frequency bin (e.g. delta, theta, etc.). We observed that AUC of low-frequency oscillations was higher at the pre-stimulation baseline for participants undergoing

DBS than controls, while those with chronic DBS did not differ from controls. This agrees with previous reports that DBS lowers theta power in individuals with dystonia. After beginning stimulation, low frequency oscillatory AUC increased, then decreased at two and three months of chronic stimulation, even though stimulation amplitude did not decrease. This pattern is only seen in the low frequencies of theta-alpha (4-12 Hz), but, not in delta (1-3), beta (13-30) or gamma (30-60) ranges. Additionally, this was not present in other sensory cortical locations, such as visual cortex. This provides evidence of oscillation reorganization in the sensorimotor circuit in response to DBS therapy, with the increase in low frequency sensorimotor cortical AUC potentially reflecting a compensatory change as the circuit adjusts to stimulation.

Disclosures: A. Alpers: None. **N. AbdAllah:** None. **K. Lizarraga:** None. **M. Gomez-Ramirez:** None. **A.L. Hewitt:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.09/D33

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

Support: R00NS110878
Tyler's Hope Foundation

Title: Striatal knockout of Gnal induces dystonia-like behavior and changes in excitability of spiny projection neurons

Authors: *N. E. CHAMBERS[1], D. HALL[1], E. MILLER[1], T. CURRY[2], I. GALLARDO[1], M. KAPLAN[1], S. GARAN[1], M. S. MOEHLE[2];
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Abstract: Dystonia is a group of movement disorders which are associated with abnormal and involuntary muscle clenching and twisting. *GNAL*-linked dystonia is a particular type of dystonia which is characterized by an adult onset and cervicospinal and limb muscle symptoms. Using a novel mouse model of *Gnal* knockout which allows for site specific *Gnal* knockout, we studied the effects of striatal *Gnal* knockout on behavior using cohorts homozygous and heterozygous for LoxP sites flanking *Gnal*. We also investigated electrophysiological properties of spiny projection neurons, and neural activity in the output pathways in the substantia nigra pars reticulata and globus pallidus externa in *Gnal* LoxP homozygous animals. We predicted that we would observe dystonia-like behaviors in these animals and that *Gnal* knockout would induce changes in electrophysiological properties of spiny projection neurons. Overall, we found that striatal *Gnal* knockout elicits dystonia-like motor symptoms which lead to hindlimb clasping and reduced motor coordination in the ledge test. Additionally, using *ex* vivo electrophysiology, we found that striatal *Gnal* knockout leads to hyperexcitability of striatal spiny projection neurons, which is reflected also in postsynaptic current recordings in substantia nigra pars reticulata and

globus pallidus interna neurons. We also found that it is likely that sodium and calcium are involved in the observed pathology, because there was an increase in rise time of the action potential and in action potential half width. Furthermore, we found changes in direct and indirect pathway activity *in vivo* using fiber photometry recordings which are related to *Gnal* knockout. Overall, these findings suggest that striatal neurons exhibit compensatory responses after *Gnal* knockout which allow movement to occur. Future studies should focus on investigating how these compensatory responses in neurons occur in the striatum and in other brain structures, with the goal of identifying novel therapeutic compounds for dystonia.

Disclosures: N.E. Chambers: None. **D. Hall:** None. **E. Miller:** None. **T. Curry:** None. **I. Gallardo:** None. **M. Kaplan:** None. **S. Garan:** None. **M.S. Moehle:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.10/D34

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

Support: R01NS075012

Title: Altered brain activation during sensory-evoked functional MRI in an animal model of DYT1 dystonia.

Authors: *R. ADURY[1], B. J. WILKES[2], P. GIRDHAR[1], Y. LI[3], D. E. VAILLANCOURT[2]; [2]Applied Physiol. and Kinesiology, [3]Neurol., [1]Univ. of Florida, Gainesville, FL

Abstract: DYT1 dystonia is a movement disorder that causes involuntary, twisting movements and abnormal postures. It is the most common inherited form of primary dystonia, caused by deletion of GAG in the DYT1 gene, encoding protein TorsinA. How this mutation and corresponding TorsinA protein dysfunction leads to brain-wide differences associated with dystonia is still unclear. Although DYT1 dystonia is classically considered a disorder of the motor system, it has been suggested that the somatosensory system plays an important role in the pathophysiology of dystonia. In this study we sought to evaluate changes to sensory and motor circuits in an animal model of DYT1 dystonia when using a thermal heat stimulus to the hind-limb. We used the dGAG knock-in (KI) model of dystonia. We performed fMRI at 11.1T using a novel sensory stimulation paradigm in dGAG KI mice (n=31) and WT littermate controls (n=28), aged 6-8 months. Our findings revealed significant differences in brain activation patterns between dGAG KI mice and WT controls. dGAG-KI mice showed significantly altered sensory-evoked brain activation in brain areas including primary motor cortex, primary sensory cortex, striatum, and substantia nigra. These findings suggest that the loss of TorsinA is associated with changes to sensorimotor circuitry, which have the potential to impact sensory processing and motor output. Understanding these changes in sensory and motor brain systems could provide insights for therapeutic targets in DYT1 dystonia.

Disclosures: R. Adury: None. **B.J. Wilkes:** None. **P. Girdhar:** None. **Y. Li:** None. **D.E. Vaillancourt:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.11/D35

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

Support: DMRF
The Michael J. Fox Foundation

Title: Single-cell transcriptomic analysis of genetic and phenotypic dystonia mouse models.

Authors: *H. DE OLIVEIRA AMARAL[1], D. FIGGE[2], D. G. STANDAERT[3], M. SCARDUZIO[4], K. L. ESKOW JAUNARAJS[5];
[1]Neurol., Univ. of Alabama at Birmingham Chapter, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [4]Neurol., UAB, Birmingham, AL; [5]Univ. of Alabama at Birmingham, Springville, AL

Abstract: Dystonia is the third most common movement disorder in the US, affecting as many as 250,000 people. This neurological disorder is characterized by sustained muscle contractions that lead to debilitating repetitive movements and abnormal postures. Dystonia is known to have many etiologies; in clinical settings it is most commonly idiopathic, but genetic forms of dystonia are increasingly recognized. We have recently found that striatal cholinergic hyperfunction is shared across three unique mouse models of genetic dystonia, THAP1 (DYT6), TOR1A (DYT1), and GNAL (DYT25). Though these mouse models do not display a recognizable behavioral phenotype, we recently characterized similar cholinergic dysfunction in a caffeine-inducible phenotypic mouse model of paroxysmal non-kinesiogenic dystonia (PNKD; DYT8). Collectively, these findings indicate that disparate genetic mutations underlying dystonia culminate in cholinergic dysfunction, though the precise interplay between ChIs and other striatal cells remains unknown. To tackle this issue, we utilized single nuclei RNA-sequencing (snRNA-seq) to establish transcriptional profiles of the effects of gene mutation on discrete populations of striatal cells in two genetic dystonia mouse models (DYT1 and DYT25). Using the same methodology, we also investigated the mutation and caffeine-induced transcriptional profiles of the DYT8 mouse model. In striata from DYT1 and DYT25, transcriptional change was minimal with the majority of differentially effected genes (DEGs) found to have reduced transcription. Pseudobulk analyses indicated downregulation of genes associated with immune responses and gliogenesis. In subpopulation analyses, genes related to cellular respiration were elevated in both indirect and direct pathway medium spiny output neurons. Likewise, mutation-dependent transcriptional change was underwhelming in DYT8 mice. However, caffeine-induced dystonia was associated with upregulated DEGs, particularly in medium spiny neurons. These data represent the first investigation of dystonia mutation-related gene transcription in mouse

models and indicate that phenotypic model development remains imperative for therapeutic target development in dystonia.

Disclosures: H. de Oliveira Amaral: None. **D. Figge:** None. **D.G. Standaert:** F. Consulting Fees (e.g., advisory boards); Abbvie Inc., Curium Pharma, Appello, Theravance, Sanofi-Aventis, Alnylam Pharmaceutics, Coave Therapeutics, BlueRock Therapeutics, Biohaven, Eli Lilly, F. Hoffman-La Roche. **M. Scarduzio:** None. **K.L. Eskow Jaunarajs:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.12/D36

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

Title: Genetic Ataxia in the Mauritanian Population: Insights from a Cohort Study

Authors: *E. EL MOUHAB;
Basic Sci., IBRO - Intl. Brain Res. Organization, Nouakchott, Mauritania

Abstract: Genetic ataxia is a debilitating condition characterized by progressive loss of coordination and balance, often resulting from inherited genetic mutations. In this study, we investigated the prevalence and characteristics of genetic ataxia in the Mauritanian population. A cohort of 78 patients, predominantly male (75%) and of Blan Moor ethnicity (85%), was examined. Among the cohort, 66.31% were of Poular ethnicity, 18.47% were Soninkés, and 15.22% were Wolofs, with a minority representing black Africans (15%). The most common form of genetic ataxia observed was Friedrich's ataxia, which displayed an autosomal recessive pattern of inheritance.Ethical considerations were paramount, with DNA extracted from whole-blood leukocytes of patients who provided informed consent. Extraction procedures adhered to rigorous standards, employing the Quagen kit methodology. This study sheds light on the prevalence and genetic underpinnings of ataxia within the Mauritanian population, contributing valuable insights for both clinical management and genetic counseling in affected communities.

Disclosures: E. El mouhab: None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.13/D37

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

Support: NIH Grant R01DC019639

Title: Cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxic dysarthria: a randomized, double-blind, sham-controlled exploratory study

Authors: S. CUST[1], **B. LAMMERS**[1], M. J. SYDNOR[1], J. L. MURTER[1], N. HARRISON[2], C. L. MARVEL[2], L. S. ROSENTHAL[2], D. C. TIPPETT[1], *R. SEBASTIAN[1];
[1]Physical Med. and Rehabil., [2]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Dysarthria is a debilitating symptom of neurodegenerative cerebellar ataxia that can negatively impact communication, social and work functions, and quality of life. No disease-modifying treatment exists for degenerative ataxic dysarthria. In this exploratory study, we applied cerebellar transcranial direct current stimulation (tDCS) as an adjuvant to speech therapy in people with neurodegenerative ataxic dysarthria. We hypothesized that cerebellar tDCS, combined with speech therapy, would enhance improvements, relative to sham stimulation (placebo) and speech therapy alone. Six patients (mean age: 56.6 years; mean symptom duration: 3.3 years; 3 females) with a diagnosis of neurodegenerative ataxic dysarthria participated in a randomized, double-blind, sham controlled, within-subject crossover trial. Patients received 5 sessions of sham stimulation plus speech therapy and 5 sessions of tDCS plus speech therapy, in random order, separated by a 1-month wash-out period. Stimulation was delivered for the first 20 min of a 1-hour speech therapy session (current = 2 mA, via carbon electrodes inserted in two 5x5 cm saline-soaked sponges, Soterix Medical 1 × 1 clinical trials device). The anode was placed over the anterior motor region of the right cerebellum and the cathode on the right deltoid muscle. All patients demonstrated notable improvements from pre-treatment to post-treatment in sham and tDCS conditions. Improvement was observed on speech intelligibility in sentences (from the speech intelligibility test); acoustic measures of duration, jitter, shimmer, mean intensity, and harmonics-to-noise ratio; speech on the Scale for Assessment and Rating of Ataxia (SARA), and functional communication skills. An important finding was that the gains on speech intelligibility in sentences, acoustic measures of duration and jitter, and as well as speech on the SARA were better maintained at the 1-month follow-up timepoint in the tDCS condition compared to the sham condition. This exploratory study suggests that cerebellar tDCS combined with speech therapy has the potential to delay progression of clinical symptoms and extend quality of life in patients with neurodegenerative ataxic dysarthria. Because of its ability to modify cerebellar excitability without significant side effects, cerebellar tDCS may be a powerful tool for speech rehabilitation associated with cerebellar dysarthria.

Disclosures: S. Cust: None. **B. Lammers:** None. **M.J. Sydnor:** None. **J.L. Murter:** None. **N. Harrison:** None. **C.L. Marvel:** None. **L.S. Rosenthal:** 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.; Site principal investigator for Biohaven pharmaceutical, EIP Pharma and Pfizer via University of Chicago. Consultant for Biohaven Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Reata Pharmaceuticals. **D.C. Tippett:** None. **R. Sebastian:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.14/D38

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

Title: Movement-related potentials recorded using cerebellar deep brain stimulation leads

Authors: U. SAHA[1], S. K. KALIA[4], J.-F. NANKOO[5], T. CORTEZ-GRIPPE[2], M. CALLISTER[6], G. SORRENTO[7], R. MUNHOZ[8], A. FASANO[3], *R. CHEN[9];
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Abstract: This study investigates cerebellar local field potentials (LFPs) associated with movement using DBS leads in patients with spinocerebellar ataxia. The Bereitschaftspotential (BP) detectable via EEG over cortical motor areas during voluntary movement is well-described, but its generative source is not established and has been hypothesized to involve widespread cortical and subcortical generators. Corresponding movement-related potentials have been recorded using DBS in deep brain structures including the subthalamic nucleus and thalamic ventrolateral nucleus. Cerebellar DBS is currently being explored as a treatment for spinocerebellar ataxia (SCA) and other movement disorders, presenting an opportunity to analyze cerebellar LFPs associated with voluntary movement. Two patients with SCA were implanted with bilateral DBS leads targeting the dentate nuclei. Prior to internalization and stimulation, patients underwent recording of LFPs from bilateral externalized leads as well as scalp EEG over Cz, C3, C4, Pz, Fz, Fp1, Fp2, and surface EMG over the extensor carpi radialis (ECR) muscles. The recording included self-paced voluntary wrist extension every 5-10 seconds for 10 minutes, one side at a time. We performed back-averaging, marking EMG bursts recorded from ECR along with EEG and LFP data. BP was present in both patients' central scalp EEG leads and the LFP data. Externalized DBS lead recording from patient 1 was limited by artifact causing frequent upward drift in all cerebellar DBS lead contacts, limiting the number of voluntary movements acceptable for back-averaging. Monopolar montage revealed a slowly rising potential in all cerebellar DBS leads in both patients, starting around 1-1.5 seconds before the voluntary wrist movement in patient 2. Bipolar montage showed phase reversal in the right cerebellum in patient 2, this was less certain in patient 1 which may be due to the drift artifact. Recordings from these first 2 patients suggest that movement-related potentials corresponding to the BP can be recorded using cerebellar DBS electrodes, similar to those seen in other deep brain structures. We anticipate recording from additional patients in the near future, expanding our analysis to include event-related synchronization and desynchronization, and investigating LFPs associated with more complex movements including motion capture measures of gait.

Disclosures: U. Saha: None. **S.K. Kalia:** None. **J. Nankoo:** None. **T. Cortez-Grippe:** None. **M. Callister:** None. **R. Chen:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.15/D39

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

Support: Natural Sciences and Engineeering Research Council of Canada RGPIN-2022-03368
Canada Research Chair CRC-2020-00079

Title: Brain structure and degeneration staging in spinocerebellar ataxia type 2 (SCA2): Magnetic resonance imaging volumetrics from the ENIGMA-Ataxia Working Group

Authors: *J. W. ROBERTSON[1], I. HARDING[2], C. R. HERNANDEZ-CASTILLO[1];
[1]Computer Sci., Dalhousie Univ., Halifax, NS, Canada; [2]Monash Univ., Melbourne, Australia

Abstract: SCA2 is a rare neuromuscular disorder in which excess repeats of the CAG triplet causes the ataxin-2 protein to misfold, causing cerebellar atrophy over time. There is no known cure for SCA2, however understanding its progression can aid in the early diagnosis and management of the disease. Currently, most studies of SCA2 suffer from limited sample size due to its rarity, necessitating a multi-site approach. Our objective was to examine the differences between a large group of SCA2 patients (n = 110) and matched healthy controls (n = 128) from ten sites around the world, both to reinforce our current understanding of SCA2-related atrophy and to cross-sectionally examine changes at different stages of the disease.
Based on T_1-weighted MRI scans, significant groupwise differences (family-wise error corrected $p < 0.05$) were observed between patients and controls throughout the brain. The strongest effects (Cohen's $d > 1.5$) were observed in the cerebellar white matter (WM), brainstem, and corticospinal tracts. The tracts leading toward the primary motor cortex, such as the internal capsule and superior corona radiata, were significant at a moderate effect size ($d > 0.5$). Strong effects ($d > 0.8$) were also observed throughout the cerebellar grey matter (GM); a functional mapping of the results found the strongest effects in areas associated with cognitive outcomes, followed by those involved in motor planning. In the cerebral GM, the accumbens, caudate, and thalamus also showed moderate ($d > 0.5$) atrophy in patients.
Regressions between clinical data and patient images revealed strong negative correlations with disease severity as measured with the Scale for Assessment and Rating of Ataxia (SARA). Significant areas again included the entire cerebellar WM and brainstem, as well as select tracts in the cerebrum, notably the premotor and supplementary motor tracts. Significant correlations also occurred in many areas of the cerebellar GM, including Lobules I-IV, VIIIa/b, IX, and Crus II.
Finally, patients were divided into pre-symptomatic (SARA < 3) and quartiles of symptomatic, with each group compared to healthy controls in turn. Tissue atrophy across the brain increased in both effect size and area with severity, especially in patients with SARA scores above the median. Notably, regions of the cerebral GM along the longitudinal fissure showed significant atrophy in the fourth quartile of patients, which was not observed in the whole-group comparison.

This study demonstrates not only that previously-understood SCA2 atrophy results hold up with a larger sample size, but that severe or late-stage disease causes atrophy in new areas throughout the motor system of the brain.

Disclosures: J.W. Robertson: None. **I. Harding:** None. **C.R. Hernandez-Castillo:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.16/D40

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

Support: RO1NS082351

Title: Role of astrocytes in SCA1 pathogenesis

Authors: *S. DATTA;
Neurol., Northwestern Univ., Chicago, IL

Abstract: Spinocerebellar ataxia1, is an autosomal dominant neurodegenerative disorder with an adult caused by an abnormal (more than 40) polyglutamine expansion in the ataxin1 protein. Mutant ataxin though expressed throughout the brain causes focal damage mainly in the cerebellum resulting in defining ataxic symptoms. The molecular hallmark of this pathogenesis is the loss of Purkinje neurons in the cerebellum and cerebellar atrophy. Increasing research in this field suggests that the other neuronal as well as the non-neuronal cell populations in the cerebellum also succumb to this adverse effect and hence SCA1 pathology is emerging as an outcome of cerebellar circuit dysfunction. Astrocytes support neuronal health and synaptogenesis. Reduced astrocytic density and diminished astrocyte and Purkinje neuron interconnections at axon initial segment in SCA1 mice cerebellum has been reported by us previously. We hypothesized that the astrocytes, the compromised non-neuronal counterpart in SCA1 cerebellar circuit play a defining role in SCA1 pathogenesis. Using iPSC derived astrocytes/neurons and SCA1 knock-in mice model we have done a detailed characterization of the astrocytes including impaired calcium signaling and ability to support synaptogenesis of neurons, affecting their firing and network properties.

Disclosures: S. Datta: None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.17/D41

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

Support: R-61

Title: Engineering Synthetic Nano-VEGF Peptide Amphiphiles as treatment for Spinocerebellar Ataxia Type 1.

Authors: *N. PANAT[1], A. METLUSHKO[2], G. GHASEMPOUR[3], S. I. STUPP[3], P. OPAL[4]; [1]Neurol., Northwestern Univ., Chicago, IL; [2]Northwestern Univ., Evanston, IL; [3]Northwestern Univ., Chicago, IL; [4]northwestern, Chicago, IL

Abstract: Spinocerebellar ataxia type 1 (SCA1) is an inherited neurodegenerative disorder with no cure. Patients typically develop a deterioration in motor incoordination resulting from cerebellar degeneration. The disease is triggered by a mutated ATXN1 gene coding for an abnormally expanded glutamine(Q) sequence. In our previous work on SCA-$1^{154Q/2Q}$ knock-in mouse model of human disease, we found genetic suppression of vascular endothelial growth factor (VEGF), which is required for blood vessel growth and neuronal health. This finding was even confirmed in human SCA1 patient autopsy samples. We further demonstrated that increasing VEGF levels genetically or through direct delivery into the spinal fluid (ICV route) in SCA-1 models significantly improved the disease phenotype (Cvetanovic et al., Nature Medicine, 2011). However, there remain significant limitations to bring rVEGF to the clinic as it is unstable, immunogenic, and expensive. We recently addressed these limitations of rVEGF by creating synthetic VEGF-mimicking nanostructures engineered from peptide amphiphiles (PAs) with Dr. Stupp's group at Northwestern. These PAs offer several advantages as they are non-immunogenic, biodegradable, and offer a cost-effective and scalable production. The current study utilizes fluorescently (TAMRA) labelled charged diluent PAs of the nano-VEGF and the PAs lacking V_2A_2 domain, which reduce their tissue aggregation. We stereo-tactically injected these PAs in the wild type C57BL/6 mice (n=3) brain parenchyma and analyzed their distribution at 24 hours using confocal microscopy at our core facility (Nikon CAM). This revealed a significantly improved tissue distribution of both the PAs over nano-VEGF whereas the PAs lacking V_2A_2 exhibited the most promising distribution. We further assessed their ability to activate VEGFR in cultured human endothelial cells, showed a promising cell viability, potent bioactivity, and a significant upregulation of VEGFR2 expression within a few minutes of their treatment. Our encouraging study paves the way for further investigation of these PAs' ability to improve the SCA-1 phenotype in our mouse models. This also holds a promise for accelerating their translation to human applications

Disclosures: N. Panat: None. **A. Metlushko:** None. **G. Ghasempour:** None. **S.I. Stupp:** None. **P. Opal:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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

Support: National Institute of Health NINDS award (R01 NS197387 to M.C.)
National Ataxia Foundation Grant to E. L.

Title: Sca1 progressively impacts the function of the motor network striatum-cerebellum

Authors: *E. LABRADA[1], M. CVETANOVIC[2];
[1]Neurosci., Univ. of Minnesota, Falcon Heights, MN; [2]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Spinocerebellar Ataxia type 1 (SCA1), is a neurodegenerative disease characterized by progressive motor impairment and severe degeneration of specific cell populations in the cerebellum. Traditionally, SCA1 research has focused on cerebellar dysfunction, but recent studies have revealed broader brain-wide impacts, including the striatum and cortex. This study aims to deepen our understanding of SCA1's impact on the motor network function in free-behaving animals. This is crucial since current knowledge about how SCA1 affects motor network function is limited, particularly during free movement. This gap in understanding hinders the development of effective treatments for SCA1, a condition with no known therapies, a life expectancy of 10 to 30 years post-onset, and a severe decrease in quality of life for affected individuals. This research aims to explore the functional changes within the motor network at different stages of SCA1 progression, using a knock-in mouse model. To investigate this, we use multichannel fiber photometry to record neuronal activity in the cerebellum, striatum, and motor cortex in healthy and SCA1-affected mice. Our results indicate reduced activity in the cerebellar nuclei neurons, the primary cerebellar output, in SCA1 mice.

Disclosures: E. Labrada: None. **M. Cvetanovic:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.19/D43

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

Title: Comparative analysis of Purkinje cell development in spastic vs. wild-type rat cerebellum

Authors: *H. BELLAFARD[1], S. GAFT[2], M. AGHOPOO[3], G. RADIONOV[3], D. SARHANGNEJAD[4], C. JACOBO[3], M. E. DE BELLARD[5];
[1]California State Univ. Northridge, Northridge, CA; [2]California State university, Nrthridge, Northridge, CA; [3]California State University, Northridge, Northridge, CA; [4]Fairmont Prep Acad., Anaheim, CA; [5]biology, Cal State Univ. Northridge, Northridge, CA

Abstract: Comparative analysis of Purkinje cell development in spastic vs. wild-type rat cerebellum

Hereditary ataxia, a distinctive neurodegenerative disorder, stands out for its early onset, affecting individuals as young as two years old. Characterized by impaired coordination and movement control, ataxia poses a significant challenge. Symptoms include gait ataxia, compromised eye and speech coordination, and hindered hand movements, often associated with cerebellar atrophy. The pathology primarily involves the degeneration of Purkinje cells, specialized neurons in the cerebellum, where minor alterations result in ataxia symptoms, yet the timeline of Purkinje cell loss remains unclear. CSUN's Han-Wistar rats, with a discovered homozygous recessive gene causing Purkinje cell loss, offer a valuable model for studying ataxia pathology. By employing immunohistochemistry staining, classic Hematoxylin Eosin histology, cell shape tracing, and quantifying neuronal density, our project aims to determine when Purkinje neuron loss begins in these rats and if the loss begins by cell degeneration as assessed by smaller cell body and dendritic tree in the Purkinje cells. This research will contribute to a deeper understanding of ataxia and its pathological progression.

Disclosures: H. Bellafard: None. **M.E. De Bellard:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.20/D44

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

Title: Homeostasis of Sphingoid Bases and Phosphates is Essential for Neuronal Health

Authors: T. S. MCCLINTOCK[1], N. KHAN[1], J. B. WOODS[1], L. ZHAO[2], ***S. SPASSIEVA**[1]; [1]Univ. of Kentucky, Lexington, KY; [2]Jackson Lab., Bar Harbor, ME

Abstract: In the brain, ceramide synthase 1 (CerS1) is expressed in the neurons. Mutations resulting in catalytically inactive CerS1 lead to an ultra-rare disease, myoclonic epilepsy with mental retardation, and to cerebellar neurodegeneration with ataxia. CerS1 deficiency results in increased levels of its substrates, the sphingoid bases and their phosphate derivatives, and in decreased levels of its products, C_{18} and $C_{18:1}$ ceramides. We developed a transgenic mouse model that decouples the downstream effects of the sphingoid bases and phosphates from the effects of ceramides. In this transgenic model, CerS2, a different ceramide synthase isoform that generates C_{22} and C_{24} ceramides, is ectopically expressed in the neurons of the CerS1-deficient mice. The CerS2 transgene rescued the neurodegenerative phenotype and restored the physiological levels of the sphingoid bases and phosphates while the levels of ceramides remained as in the mutant. These data indicated that the primary cause of the neurodegenerative phenotype is elevated above physiological levels sphingoid bases and/or their phosphates. We used these mouse models to study the function of the sphingoid bases and phosphates in neuronal health. Our RNA-seq data from mouse cerebella showed that loss of function of CerS1

significantly changed the cerebellar transcriptome in ways that provide evidence of progressive Purkinje cell neurodegeneration, possible delay in interneuron maturation and activation of microglia. In addition, immunofluorescence data in CerS1-deficient mice corroborated the transcriptome findings for Purkinje cells neurodegeneration and activation of glial cells in the cerebellum and cortex. Moreover, our *in vitro* data showed that co-culture with CerS1 mutant neurons resulted in an increased activation state of wild type microglia. Our data suggest that the homeostasis of sphingoid bases and their phosphates, in the neurons is essential for neuronal health and, if dysregulated can lead to neurodegeneration and induce glial activation. Moreover, our results can contribute to deciphering the role of sphingoid bases and their phosphates in more complex neurodegenerative deceases such as Alzheimer's disease or cerebellar ataxias where sphingoid bases were shown to be elevated.

Disclosures: T.S. McClintock: None. **N. Khan:** None. **J.B. Woods:** None. **L. Zhao:** None. **S. Spassieva:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

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

Support: NINDS MOSAIC 1K99NS130151-01A1
NINDS R37 NS054154-14

Title: An ENU-induced mouse model of autosomal dominant spastic ataxia

Authors: *T. J. HINES[1], J. R. FUNKE[1], S. L. PRATT[2], R. W. BURGESS[1];
[1]The Jackson Lab., Bar Harbor, ME; [2]Jackson Lab., Bar Harbor, ME

Abstract: A novel mouse model of autosomal dominant spastic ataxia was isolated from an ENU mutagenesis screen for neurological phenotypes. The index case was a male C57BL/6J mouse exhibiting muscle wasting and an intention tremor starting at approximately 4 weeks of age, which progressed to severe ataxia by 6 weeks of age. Due to difficulties breeding, the line was propagated via IVF with BALB/cByJ oocyte donors for genetic mapping. Further characterization of the mouse line has revealed that body affected and unaffected littermates are virtually indistinguishable (i.e. no tremor, similar body weights) before 4 weeks of age. This is followed by rapid degeneration of cerebellar Purkinje neurons, numerous skeletal muscle defects (e.g. necrotic fibers, central nuclei, ringbinden, etc.), disrupted transmission at the neuromuscular junction, decreased bone density, and reduced lifespan. Interestingly, Purkinje neurons in lobule X are spared. The causative mutation was mapped to a 25 mb region on Chr 1 and whole exome sequencing revealed a promising missense SNP in the serine threonine kinase 36 gene (Stk36Y1003N), which segregates perfectly with the phenotype. However, when this mutation was engineered into a mouse line, no discernible phenotypes were observed. Whole genome

sequencing is currently being carried out to identify other promising candidate mutations, which we will test with CRISPR-engineered mouse lines.

Disclosures: T.J. Hines: None. **J.R. Funke:** None. **S.L. Pratt:** None. **R.W. Burgess:** None.

Poster

PSTR454: Ataxias and Dystonias: Models and Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR454.22/D46

Topic: C.06. Neuromuscular Diseases

Support: NIH Small Grant Program (R03)

Title: Frataxin gene targeted-histone demethylation contracts expanded GAA repeats in Friedreich's ataxia

Authors: *H. A. BRAVO GALLEGOS, R. ARMBRISTER;
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Abstract: Friedreich's Ataxia (FRDA) is the most common autosomal recessive neuromusculardisorder and caused by expanded GAA repeats in the first intron of the frataxin (*FXN*)gene. No effective treatments for the disease are available. Thus, a treatment that targetsthe expanded GAA repeats is urgently needed. We recently found that the inhibition ofH3K9 trimethylation (H3K9me3) synergized with DNA base excision repair (BER) tocontract the expanded GAA repeats and upregulate *FXN* gene expression in FRDA neuralcells and transgenic mouse brain tissue. We further hypothesize that GAA repeat-targeteddemethylation of H3K9me2/me3 at the *FXN* gene can disrupt heterochromatin and induceBER to contract the expanded repeats. To test this hypothesis, we constructed the *FXN*gene-targeted CRISPR/deadCas9 (dCas9) plasmids with the histone H3-trimethyl-L-Lysine 9 demethylase 4D (KDM4D) fused to catalytically inactivated S. pyogenes Cas9(CRISPR/dCas9-KDM4D) and transfected them into FRDA neural cells to inducedemethylation of H3K9me2/me3 on the expanded GAA repeats in FRDA neural cells. Ourpreliminary results showed that FRDA neural cells with the *FXN* gene-targetedCRISPR/dCas9-KDM4D exhibited the contraction of the expanded GAA repeats,suggesting that the *FXN* gene-targeted histone demethylation resulted in GAA repeatcontraction. Using molecular dynamics simulation, we further revealed how thesecontractions were facilitated and how the BER repair enzymes cross-talked with theepigenetic shift that our CRISPR/dCas9-KDM4D creates. Our study has provided proofof concept for a gene-targeted contraction of expanded GAA repeats via the synergybetween histone modifications and DNA repair. Our study will further open a new avenueto develop an effective gene therapy for FRDA.

Disclosures: H.A. bravo gallegos: None. **R. Armbrister:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.01/D47

Topic: B.09. Glial Mechanisms

Support: RF1NS131110

Title: Connecting Form and Function: Mapping Microglial Spatial Biology in a Mouse Model of Acute and Chronic Ischemic Stroke.

Authors: K. YOUNG[1], A. HECK[1], A. ROSENBLOOM[1], A. WARDHANI[1], M. WALTER[1], R. LIU[1], L. WU[1], C. WILLIAMS[1], M. HOANG[1], J. BEECHEM[1], K. P. DOYLE[2], *H. MORRISON[3];
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Abstract: As the primary immune cells of the brain, microglia are extremely sensitive to changes in their environment, engaging in intricate communication networks that involve the exchange of small molecular signals that allow them to adapt their behavior based on a variety of stimuli in their vicinity. These shifts in functional behavior, from surveillance to injury response, may be associated with morphological changes, which may serve as markers of their functional state. To our knowledge, few have combined spatial proteomics and traditional immunohistochemistry (IHC) to map microglial form and function in situ following an ischemic stroke. Our study uses cutting edge spatial biology tools to track microglial functional dynamics after ischemic stroke combined with a morphometric analysis at acute and chronic timepoints. Male mice (16 weeks old) were subjected to transient middle cerebral artery occlusion (tMCAO) and reperfusion using the filament method. Following the tMCAO procedure and MRI confirmation of injury, brain tissue was collected at 3 timepoints (24hr., 2 weeks, and 4 weeks post-stroke), fixed, cryoprotected, and sectioned for spatial proteomics (SP) and IHC methods. Tissue sections (SP: 10µm & IHC: 50µm) at ~ bregma -1 were used for data collection within the ipsilateral and contralateral hemispheres at consistent regions of interest (ROI) spatially oriented to the infarct (e.g. infarct core, adjacent, and distal). Proteomic data were collected within ROIs and across the 3 timepoints using the CosMx^{TM} Spatial Molecular Imager (SMI) platform to detect up to 68 proteins at the single cell level. Briefly, the proteomic assay detects proteins with oligonucleotide barcode-conjugated antibodies and each analyte relies on barcode readout on the SMI instrument via several rounds of reporter binding and fluorescence imaging. Microglia morphologies within ROIs were quantified using skeleton and fractal analysis methods. Proteomic and morphometric data were analyzed and used to provide a comprehensive view of microglial spatiotemporal morphologic and functional responses at acute and chronic timepoints post-stroke. By utilizing the SMI platform and the high plex CosMx^{TM} Mouse Neuroscience Protein Panel, we gain a more complete view of the complex interactions that occur between neuronal and glial cell types and how these interactions change depending on proximity to the infarcted core across different post-stroke timepoints. Additionally, by pairing

the spatial proteomic data with microglial morphology analysis, we gain further insight into microglial form and function correlations within the spatiotemporal context of ischemic stroke.

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Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.02/D48

Topic: B.09. Glial Mechanisms

Support: NIH R01 NS102365

Title: Up Regulation of the Engulfment Receptor Jedi-1 in Cerebral Vascular Cells and Microglia Following Stroke Injury

Authors: *B. A. HERNANDEZ[1], M. G. HOUPERT[1], Y. CHEN[2], R. R. RATAN[3], B. D. CARTER[1];
[1]Dept. of Biochem., Vanderbilt Univ., Nashville, TN; [2]Dept. of Neurol. and Neurosciences, Weill Med. Col. of Cornell Univ., Burke, White Plains, NY; [3]Burke Neurolog. Inst., White Plains, NY

Abstract: Microglia are the resident immune cell of the central nervous system (CNS), responsible for the phagocytosis of dead cells that arise during development or due to injury or disease. Likewise, cerebral vasculature plays a critical role in the repair processes that take place following injury or disease. As such, understanding the mechanisms by which microglia regulate their phagocytic activity and how blood vessel vascular reorganization is mediated is necessary for a better understanding of their functions in diseased states. The engulfment receptor Jedi-1 (PEAR1/MEGF12) is involved in the phagocytic clearance of dead neurons by satellite glia in developing dorsal root ganglia. Jedi-1 is also expressed by endothelial cells of blood vessels and restricts their proliferation. Recently, the Carter lab found it is also expressed by microglia in the postnatal (P7) mouse, neurogenic, ventricular-subventricular zone (V-SVZ). Deletion of Jedi-1 in microglia reduced their phagocytic ability and resulted in a shift to a pro-inflammatory phenotype, leading to suppression of neurogenesis. To determine whether Jedi-1 has a role in microglial response to pathological conditions, we investigated its expression following ischemic stroke. We performed immunostaining for IBA1, labeling microglia, and Jedi-1 under basal conditions in the adult mouse brain. We found Jedi-1 expressed by 29.9.2 ± 2.4% of the V-SVZ microglia in the adult, compared to 46.6 ± 2.3% of Jedi-1^{+} V-SVZ microglia at P7. We hypothesized that following a stroke injury, where apoptosis would be increased, Jedi-1 will be upregulated. Adult wild-type mice underwent a transient Middle Cerebral Artery occlusion, or sham surgery, followed by reperfusion and brain tissue samples were gathered at 3- and 7- days post injury (dpi). Our results showed a significant increase in Jedi-1^{+} microglia in the cortex at both time points following stroke (from 7.4 ± 1.9% in sham treated to 24 ± 3.1% 3dpi and 8.4 ± 1.7% sham to 56.2 ± 2.3% 7dpi). Contrastingly, microglia in the V-SVZ upregulated Jedi-1 beginning only at 7dpi (35.4 ± 2.9%). Jedi-1 expression was also dramatically upregulated in vascular cells, indicated by laminin staining, 7 days after stroke injury. The results suggest that Jedi-1 plays a role in the microglial and vascular response to stroke. Future studies will investigate the specific function of Jedi-1 in these cells after stroke, which will provide a clearer understanding of how microglia and brain vascular reorganization can be employed to benefit the post-injury brain.

Disclosures: B.A. Hernandez: None. **M.G. Houpert:** None. **Y. Chen:** None. **R.R. Ratan:** None. **B.D. Carter:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.03/D49

Topic: B.09. Glial Mechanisms

Support: NIH R21EB028055
NIH R44MH131514

Title: Low-intensity pulsed ultrasound reduces the activation of microglia at the tissue electrode interface and increases chronic recording yield.

Authors: *K. W. GHERES[1], J. K. GREASER[2], J. GALLEGO[3], R. B. BAGWELL[1], T. D. KOZAI[4], M. L. MULVIHILL[2];
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Abstract: Chronically implanted silicon shank electrodes induce vascular hemorrhage, cell lysis, and tissue deformation at the implant site. This perturbation initiates a chronic injury response in both neurons and microglia with morphological changes to microglia being observed within minutes following implant. Reactive microglia amplify the injury response by activating astrocytes and recruiting macrophages. Therefore, methods to reduce microglial activation and attenuate chronic inflammation hold significant promise for improving the chronic viability of implanted neural electrodes.
Trans-cranial focused ultrasound (tFUS) has recently evolved as a non-invasive method to regionally modulate synaptic and non-synaptic mechanisms of neuron and glial cell activity. Previous research has demonstrated neuroprotective and anti-inflammatory effects of tFUS in traumatic brain injury and neurodegenerative disease models. We investigated whether the neuroprotective effects of tFUS could reduce microglia reactivity and preserve electrophysiological measures of neural activity in a rodent model using chronically implanted silicon shank electrodes. We developed a reusable head-mounted low-intensity pulsed ultrasound (LIPUS) delivering device to investigate the effects of tFUS on the activation of microglia across the first post-operative month and the relationship between microglial activity and single-unit recording yield of implanted electrodes. Periodic (15 min/day) LIPUS treatment was delivered around electrodes followed by in vivo electrophysiology and two-photon microscopy to assay neural activity and microglia reactivity. Treatment frequency and duration was varied over the course of the post-operative recording period to determine whether LIPUS delivery is required for the duration of the recording period or if treatment in the acute post-injury phase is sufficient to maintain implant patency.
Our in vivo experiments demonstrate that periodic treatment with high frequency (~1MHz) LIPUS alters microglia migration velocity and timing compared to untreated controls and that cellular encapsulation of electrodes is reduced in subjects receiving LIPUS treatment. Single unit recordings of neural activity in subjects receiving LIPUS treatment demonstrated an increase in electrode impedance, greater signal-to-noise ratios, and more identifiable single units across a greater number of electrode channels compared to control subjects. These results demonstrate the validity of tFUS for modulation of microglia and suppression of the FBR and provide a device for simplified non-invasive modulation.

Disclosures: K.W. Gheres: A. Employment/Salary (full or part-time):; Actuated Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

holder, excluding diversified mutual funds); Actuated Medical Inc. **J.K. Greaser:** A. Employment/Salary (full or part-time):; Actuated Medical Inc.. **J. Gallego:** None. **R.B. Bagwell:** A. Employment/Salary (full or part-time):; Actuated Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical Inc.. **T.D. Kozai:** None. **M.L. Mulvihill:** A. Employment/Salary (full or part-time):; Actuated Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical Inc..

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.04/D50

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

Title: Exploring the Impact of Low-Dose Tissue Plasminogen Activator on Microglia-Mediated Inflammation: Implications for Ischemic Stroke Complications

Authors: *D. A. ALMARGHALANI;
Taif Univ., Taif, Saudi Arabia

Abstract: Tissue plasminogen activator (tPA) is a widely used thrombolytic treatment for acute ischemic stroke. However, tPA administration is associated with the risk of inflammation and potentially converting ischemic stroke into hemorrhagic stroke. Microglia, the intrinsic immune cells of the central nervous system, play a vital role in regulating inflammatory responses after ischemic stroke. Previous studies revealed that tPA administration at high doses can exacerbate neuroinflammation by activating microglia and promoting the release of pro-inflammatory cytokines, subsequently causing more neuronal damage. However, there are limited studies on the effects of low doses of tPA on inflammation in microglia. Thus, this study investigated whether low doses of tPA could modulate the inflammation in the human microglial clone 3 (HMC3) cell line challenged with thrombin, which mimics the risk of hemorrhagic transformation associated with tPA treatment. Additionally, we examined the effects of tPA on HMC3 challenged with lipopolysaccharide (LPS). HMC3 cells were subjected to thrombin (500 U/ml) as in *vitro* model for hemorrhage, or LPS (100 ng/mL), and treated with different low doses of tPA (2, 5, 10, 20, 50, and 100 ng/mL). We assessed the release of pro-inflammatory markers, such as nitric oxide (NO), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α), as indicators of microglia-mediated inflammation. Our findings demonstrated that microglia challenged with thrombin or LPS exhibited a significant increase in NO, IL-1β, and TNF-α levels. However, treatment with low doses of tPA resulted in a dose-dependent reduction in the release of pro-inflammatory markers, including nitric oxide, IL-1β, and TNF-α. These findings indicated that low doses of tPA potentially reduced inflammation in microglia when exposed to thrombin or LPS. Further investigations are warranted to unravel the underlying mechanisms through which tPA modulates microglia-mediated inflammation. In addition,

understanding the impact of low-dose tPA on microglia-mediated inflammation in the context of thrombin and LPS challenges provides valuable insights into the complex interplay between thrombolytic therapy, microglia activation, and stroke complications. This knowledge holds promise for the development of improved treatment strategies and guidelines, aiming to optimize the use of tPA in the management of acute ischemic stroke while reducing the risk of inflammation.

Disclosures: D.A. Almarghalani: None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.05/D51

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

Support: Canadian Institutes of Health Research (CIHR)
Heart and Stroke Foundation of Canada
VAST Doctoral Scholarship Award

Title: Measuring circulating microglia derived extracellular vesicles post-stroke in the rat

Authors: *H. P. MARTIN[1], S. N. WHITEHEAD[1], J. D. EDWARDS[2];
[1]The Univ. of Western Ontario, London, ON, Canada; [2]Univ. of Ottawa Heart Inst., Ottawa, ON, Canada

Abstract: Background: Chronic activation of proinflammatory microglia is associated with increased stroke infarct volume and poorer cognitive consequences. Current screening tools to measure microglia *in vivo* and longitudinally are inaccessible, pose safety concerns, or lack specific markers to distinguish diverse microglia activation phenotypes. Extracellular vesicles (EVs), on the other hand, retain cell-specific surface markers, can cross the blood brain barrier, and be detected in blood plasma samples. We hypothesized that circulating EVs released from microglia (MEVs) are elevated post-stroke and will be associated with stroke-lesion size. To test this hypothesis, we used nanoflow cytometry, which can measure particles smaller than 500 nm in diameter to quantify and differentiate MEV activation phenotypes and determine whether MEVs are associated with stroke volume. **Methods**: To induce transient focal ischemic stroke, 5-month male and female Fischer 344 rats (n=10) were randomly assigned to stereotaxic injection of either 60 or 600 pmol endothelin-1, a potent and transient vasoconstrictor, in 3 µL of saline into the right dorsal striatum. Saline injection was given to control rats. Blood plasma was isolated at baseline as well as longitudinally at 24-hours, 3-days, and 7-days post-stroke. Based on published protocols developed in our lab, nanoflow cytometry was used to directly detect and measure MEVs in blood plasma samples. Circulating MEVs were identified using fluorescently tagged antibodies against TMEM119 and various microglia activation phenotypes. Stroke infarct volumes were measured in post-mortem brain tissue using immunohistochemistry labelling with

NeuN antibody. **Results**: MEVs were successfully labelled and identified in rat plasma samples pre- and post-stroke. Ongoing investigations will determine if various MEV surface markers, along with their cargo are associated with stroke-lesion size. **Conclusions**: This study seeks to develop a new platform for the early detection of post-stroke cognitive impairment using plasma-based markers of microglia activation *in vivo*. Given that infarct volume plays a role in determining stroke severity and functional outcomes, future directions aim to interrogate whether circulating MEVs can discriminate cognitive domains and predict cognitive decline following stroke.

Disclosures: H.P. Martin: None. **S.N. Whitehead:** None. **J.D. Edwards:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.06/D52

Topic: B.09. Glial Mechanisms

Support: National Natural Science Foundation of China (Nos.82174499)
National Natural Science Foundation of China (Nos.82130032)
National Natural Science Foundation of China (Nos.31930042)

Title: Microglial phagocytic mechanism plays a critical role in the disrupted neuron connection of medial prefrontal cortex of comorbid symptoms in chronic pain

Authors: *L. LIANG[1], J. YU[2], Y.-Q. ZHANG[3];
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Abstract: Abstract Background: Comorbid depressive symptoms (CDS) in chronic pain is usually reported in clinic. According to clinical study, depressive symptoms usually lead to the increasing intensity and duration of pain. The patients with CDS would be more difficult to recover. An effective treatment for CDS with chronic pain is needed. The function and structure of rodent medial prefrontal cortex (mPFC) has been reported to be altered in depression animal model. It was also reported to be involved in processing of some clinical pain models, such as spared nerve injury (SNI) and chronic constriction injury of the infraorbital nerve (CION). The mPFC is organized into several layers, it mainly consists of pyramidal neuron (PNs) and GABAergic interneurons (INs). The CDS in chronic pain is usually related to the disrupted functions of mPFC. Microglia are macrophages of the central nervous system (CNS). In the past few years, many studies reported that under pathological conditions, the microglial phagocytic mechanism affects the neuron synapses which leads to disrupted connections between neurons. Studies shown that the CION model can leads to anxiety- and depression-like behavior. Our previous studies have confirmed that the microglia shown a morphological change in mPFC of the CION model mice. Therefore, the microglia functions may relate with the pathological

phenotypes of CION model and the functions of mPFC. But its potential mechanism (including how the microglia functions affect the neuron connection in mPFC) remains unknown. **Method:** In this study, we first established a mice model of CION. Von Frey, Forced swimming test (FST),Open Field Test (OFT) and Elevated plus maze test (EPM) were used to evaluate the phenotypes of CION models. The Immunofluorescence (IF) was used to evaluate the microglia morphology. Whole-cell recording was used to measure the electrophysiological change of mPFC neuron. RNA sequencing was used to find out the factors leading to the change of microglia. By virus expression in brain , to explore how the microglia affects the neuron functions in mPFC. **Result:** (1) Microglia morphology changed of in mPFC of CION model mice. (2) Inhibition of the microglia improved the anxiety and depression behavior of CION. (3) Inhibition of the microglia can change the PNs activity in specific mPFC layers. (4) Microglial phagocytic function mediates the electrophysiological excitatory/inhibitory (E/I) balance change in specific layer of mPFC.**Conclusion:** Our study proved that microglia phagocytic function leads to the (E/I) changed in mPFC and then mediates the function change of mPFC which will forms a complex phenotypes of CION model.

Disclosures: L. Liang: None. **J. Yu:** None. **Y. Zhang:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.07/D53

Topic: B.09. Glial Mechanisms

Support: K08NS114170
R01NS129609

Title: Satellite microglia are a marker of chronic injury in human brain trauma

Authors: *K. SYTSMA, A. FEICHTENBINER, A. NOLAN;
Dept. of Lab. Med. and Pathology, Univ. of Washington, Seattle, WA

Abstract: Traumatic brain injury is a risk factor for dementia and neurodegenerative disease (NDD), but the mechanisms occurring between early life TBI and later NDD development are unknown. Furthermore, few neuropathology studies have examined the neuropathology of TBI before NDD has fully developed, skewing our knowledge. Given the proposed mechanisms of toxic protein production and neuroinflammation as possible initiators or contributors to progressive pathology, we examined phosphorylated tau accumulation, microgliosis and astrogliosis using immunostaining in the orbitofrontal cortex, a region often vulnerable across TBI exposures, in an age and sex-matched cohort of community TBI including both mild and severe cases in midlife (average age 49). These cases had little neurodegenerative pathology affecting the neocortex, except for the presence of mild chronic traumatic encephalopathy in 30-40% of TBI cases. The percent area of staining in the grey matter for AT8 (phosphorylated tau),

IBA-1 (microglia and macrophages), CD68 (lysosome marker, associated with more phagocytic microglia/macrophages) and GFAP (astrocytes) was determined and compared across matched control, mild TBI (mTBI) and severe TBI (sTBI) cases. A significant difference was identified for IBA-1 and AT8 by repeated measures one-way ANOVA testing ($p = 0.0086$ and 0.0464, respectively); post-hoc analysis specifically found an increase in the sTBI compared to the control group. These differences remained significant only for IBA-1 staining with removal of cases with CTE pathology from analysis ($p=0.0205$, one-way ANOVA). When analyzing the IBA-1 images, we noticed not only an increase in staining, but that many microglia appeared to be situated next to neurons- ie. perineuronal satellite microglia (Sat-MG). To confirm this impression, we analyzed 3D immunofluorescent confocal images, and found increased neurons with satellite microglia in both mild and severe TBI compared to controls, with or without CTE cases included. Reconstruction analysis with Imaris found differential changes in morphology with injury, supporting perhaps a unique role for this subtype. Further studies are needed to understand this unique relationship and how satellite microglia might contribute to neuronal function and progressive changes in physiology after TBI.

Disclosures: K. Sytsma: None. **A. Feichtenbiner:** None. **A. Nolan:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.08/Web Only

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

Title: Large Language Models for efficient classification and automatic explanation of microglia activation in mouse brains

Authors: *P. R. MOUTON[1], A. KANDIYANA[2], G. J. HARRY[4], L. HALL[3], D. GOLDGOF[3]; [1]Computer Sci. & Engin., SRC Biosci. and USF, Tampa, FL; [2]Dept. of Computer Sci. and Engin., [3]Computer Sci. & Engin., Univ. of South Florida, Tampa, FL; [4]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC

Abstract: Microglia cells play a central role in developmental and immune functions in neural tissues and undergo activation in traumatic brain injury, neurotoxic exposures, age-related neurodegenerative diseases, and other neurological disorders and mental illnesses. The most reliable methods for assessing number and activation state require manual counting (clicking) and rating of hundreds of highly magnified microglial cells in stained tissue sections through defined regions of interest in each case. Limitations include low efficiency and inter-rater and inter-lab variation from human factors (subjectivity, training, experience, fatigue). We previously proposed convolutional neural networks (CNN) for automatic classification of microglial activation in Iba-1 immunostained sections through the hippocampus of mouse brains treated with saline (n=5) or the toxin tri-methyl tin (TMT 2mg/kg) (n=6). Ground truth was optical fractionator (stereology) counts of Iba1-immunostained microglial cells in hippocampus of each

brain (total n=11) with each count linked to low-power (20x) images of microglia in the same hippocampus. Using these low-mag images labeled with global stereology counts as ground truth, we trained a CNN to automatically predict the correct class (Saline, TMT) using only low-power images from test cases. A cross-validation “leave-one-out” strategy allowed use of all 11 cases for training and testing. The findings showed high accuracy (10/11 correct) for automatic prediction of treatment group, without cell-level segmentation or manual stereology. Limitations included the need for extensive image data and stereology-based ground truth. Here we propose three novel approaches with state-of-the-art GPT4 (OpenAI) to achieve comparable accuracy while overcoming the limitations of both manual stereology and automatic classification. We used GPT-4, a multi-modal Large Language Model (LLM), to predict the treatment group for the same n=11 cases. Rather than training with images from each class, input to GPT-4 was minimal ground-truth text (prompts) using Visual Question Answering (VQA). This GPT-4 approach showed 91% accuracy (10/11 correct) for prediction of treatment group (TMT, Saline), i.e., same as baseline method, with 50X less time and nominal images, technician effort and computation costs. Second, we introduce a novel human-in-the-loop approach using GPT-4 to automate the selection of example images as input prompts to generate explanatory text for separation of images into distinct classes. Finally, we contrast and compare techniques for in-context learning as enhanced prompts for automatic classification of new datasets.

Disclosures: P.R. Mouton: A. Employment/Salary (full or part-time):; SRC Biosciences, Stereology Resource Center. **A. kandiyana:** None. **G.J. Harry:** None. **L. Hall:** A. Employment/Salary (full or part-time):; University of South Florida. **D. Goldgof:** A. Employment/Salary (full or part-time):; University of South Florida.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.09/D54

Topic: B.09. Glial Mechanisms

Support: MDTA NIH NIDA 5P30DA048742-04
College of Pharmacy of the University of Minnesota
The Graduate School of the University of Minnesota

Title: Sex-specific mobilization of peripheral immune cells to the dorsal horn in female mice by the inhibitory neuromodulator, agmatine

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Abstract: The opioid epidemic underscores the urgent need for novel analgesic therapeutics. The pathologies of chronic pain and opioid addiction rely on activation of the N-methyl-D-aspartate (NMDA) receptor to transition acute to chronic pain and controlled substance use to uncontrolled use, respectively. Moreover, it has been proposed that centrally resident microglia, and their peripheral counters, infiltrating macrophages/monocytes, are involved in the initiation, maintenance, and resolution of chronic pain, however their functional delineation is far from concrete.
Agmatine, an endogenous inhibitory neuromodulator, antagonizes the NMDA receptor, inhibits nitric oxide synthase, prevents opioid self-administration, opioid analgesic tolerance, and the development of chronic hypersensitivity in rodents. Interestingly, we have observed that agmatine administration produces a significant increase in immune cell expression in the spinal cord dorsal horn of female subjects only, independent of disease state or drug exposure. It remains unclear if the elevation of immune cells reflects a proliferation of centrally resident microglia or an infiltration of peripheral macrophages/monocytes to the CNS. The objective of this study is to characterize the origin of immune cells observed in the spinal cord after agmatine administration using the resident-specific microglial marker, TMEM119.
Female ICR CD-1 mice (21-30 g) were intrathecally administered (5 ml) with either 30 nmol agmatine or saline. Within each group of mice, half were administered complete Freund's adjuvant (CFA) into the left hind paw to induce an inflammatory state. Spinal cords were prepared for immunohistochemical analysis with TMEM119. TMEM119 immunoreactivity (-ir) was quantified through % area of lumbar dorsal horn fluorescence intensity.
CFA-treated female mice treated with agmatine showed a significant decrease in TMEM119-ir in the lumbar spinal cord dorsal horn as compared to CFA-treated female mice treated with saline ($p=0.0004$) and control mice treated with saline ($p=0.0074$). Control female mice treated with agmatine showed a lesser, but significant, decrease in TMEM119-ir when compared with CFA-treated female mice injected with saline ($p=0.036$). No significant differences were found between saline-treated control mice and CFA-treated mice treated with saline, although there was a trend towards increase with inflammation. These data further delineate sex-differences in neuroimmune interactions under conditions of inflammation by showing that agmatine mobilizes peripheral immune cells in female mice which may contribute to the effects of agmatine in the CNS.

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Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.10/D55

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

Support: NIH ES033462
NIH ES024745

Title: Impact of chlorpyrifos (CPF) and metabolite 3,5,6-trichloro-2-pyridinol (TCPy) on inflammatory signaling in microglia

Authors: *E. N. FIKSE[1], K. BIGGS[2], F. ANDERSON[2], S. CHO[1], A. KETTENBACH[3], M. C. HAVRDA[2];
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Abstract: Exposure to agricultural chemicals increases the risk of neurodegenerative disorders, including Alzheimer's (AD) and Parkinson's disease (PD). Chlorpyrifos (CPF) is an organophosphate chemical widely used in agricultural settings until being broadly banned in 2021. CPF exposure is linked to AD and PD risk and remains an important consideration in an aging population exposed to CPF prior to reductions in its application. CPF has a half-life of 60-120 days in the environment, yielding several metabolites, including chlorpyrifos oxon (CPO) and 3,5,6-trichloro-2-pyridinol (TCPy). The CPO metabolite is more toxic than parental CPF; however, TCPy is more persistent in the environment and patients, where TCPy can be detected in urine to indicate CPF exposure. Pesticide-driven cell stress triggers sterile inflammation mediated in part by the microglial NLRP3 inflammasome. We exposed wild-type and *Nlrp3-/-* mice to CPF-contaminated drinking water throughout their lifespan to determine the impact on neuroinflammation. CPF rapidly degraded in drinking water where CPF, CPO, and TCPy were detected at similar levels within 72 hours. In CPF-contaminated water-intoxicated mice, only TCPy was detectable in the plasma. Exposure to CPF-contaminated water increased ambulatory activity in aging wild-type mice but exacerbated age-related motor decline in *Nlrp3-/-* mice. Spatial learning and memory were normal in CPF-exposed WT mice but impaired in similarly treated *Nlrp3-/-* animals. We observed increased microgliosis in CPF-treated *Nlrp3-/-* mice, not seen in their WT counterparts. To further explore the microgliosis phenotype, wild-type and *Nlrp3-/-* primary microglia cultures were exposed to CPF and TCPy, seeking evidence of inflammatory toxicity using tandem-mass tag proteomics. We found that TCPy alone elicited related but distinct changes in the microglial secretome compared with CPF, indicating a TCPy-specific inflammatory reprogramming of the cells. Further interrogation of the proteomic data noted increased haptoglobin release in TCPy-exposed *Nlrp3-/-*cultures. We confirmed increased haptoglobin release from *Nlrp3-/-* microglia cultures exposed to TCPy compared to identically treated WT cultures. Our data indicate that TCPy persists in vivo and has a specific toxicity profile in microglia. We identify haptoglobin release as a component of a parallel or compensatory inflammatory response in mice harboring germline inactivation of *Nlrp3*.

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Poster

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Program #/Poster #: PSTR455.11/D56

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

Support: F31AA030213
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R21AA026295
R21AA026295
R00AA025386
R00AA025386-S1

Title: Translational Inhibition of NF-kB/NLRP3 by Nanoligomer Mitigates Advanced Age- and Ethanol-Related Microglia Activation and Associated Markers of Neurodegeneration

Authors: *P. E. ANTON[1], S. TWARDY[2], P. NAGPAL[3], J. A. MORENO[4], M. BURCHILL[5], M. BURCHILL[5], N. BUSQUET[6], M. H. MESCHES[7], E. KOVACS[2], R. MCCULLOUGH[2]; [1]The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Sachi Bio, Louisville, CO; [4]Colorado State Univ., Fort Collins, CO, ; [5]Univ. of Colorado - Anschutz Med. Campus, Aurora, CO, ; [6]Univ. of Colorado - Anschutz Med. Campus, Denver, CO, ; [7]SciTechEdit International, LLC, Aurora, CO.

Abstract: Binge alcohol use is increasing among aged adults (>65 years). Our group, and others, have established that the brains of aged rodents are vulnerable to ethanol-related microglia reactivity and neurodegeneration compared to young rodents. However, the molecular underpinnings of this age-related sensitivity to alcohol are not well described. Heightened activation of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Nod like receptor 3 (NLRP3) mediate microglia activation and associated neuronal injury in other models of neurodegenerative disease. Therefore, we hypothesize NF-κB and NLRP3 are key mediators of enhanced ethanol-induced microglia reactivity and neurodegeneration occurring with advance age. Using a model of intermittent binge ethanol exposure in young an aged mice, we report binge ethanol increased the proportion of $NLRP3^+$ microglia in the hippocampus of aged (18-20 months) female C57BL/6N mice compared to young (3-4 months). In primary microglia, ethanol-induced expression of reactivity markers and NLRP3 inflammasome activation markers were more pronounced in microglia from aged mice compared to young. Making use of a NLRP3-specific inhibitor (OLT1177) and a novel brain-penetrant Nanoligomer that inhibits NF-κB and NLRP3 translation (SB_NI_112), we find that ethanol-induced microglial reactivity can be attenuated by OLT1177 or SB_NI_112 in primary microglia from aged mice. *In vivo,* SB_NI_112 also prevented binge ethanol-related microglia reactivity, IL-1β production, and tau hyperphosphorylation in the hippocampus of aged mice. These data suggest early indicators of neurodegeneration occurring with advanced age and binge ethanol exposure are NF-κB- and NLRP3-dependent. Further investigation is warranted to explore the use of targeted immunosuppression via Nanoligomers to attenuate neuroinflammation after alcohol consumption in the aged.

Disclosures: P.E. Anton: None. **S. Twardy:** None. **P. Nagpal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sachi Bio. **J.A. Moreno:** None. **M. Burchill:** None. **M. Burchill:** None. **N. Busquet:** None. **M.H. Mesches:** None. **E. Kovacs:** None. **R. McCullough:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.12/D57

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

Support: RO1NS14130

Title: Functional coupling between kv1.3 potassium channels and interferon induced STAT signaling in microglia.

Authors: *R. KUMARI[1], A. BRANDELLI[1], C. BOWEN[2], H. WULFF[3], S. RANGARAJU[4]; [1]Yale Univ., new haven, CT; [2]Ctr. for Neurodegenerative Dis., Emory Univ., Atlanta, GA; [3]Pharmacol., Univ. of California,, Davis, CA; [4]Neurol., Emory Univ., ATLANTA, GA

Abstract: Microglia are major enactors of neuroinflammation across several neurological disorders where they play causal roles in driving disease pathogenesis. Accumulating evidence suggests that the voltage-gated potassium channel Kv1.3 is important for regulation of pro-inflammatory and deleterious responses of microglia in neurodegeneration. Recently, using proximity labelling coupled mass spectrometry approach we identified several protein-protein interactors of Kv1.3 channels in microglia, including STAT proteins which are key regulators in interferon signaling. In this study, we aim to functionally validate these interactions of Kv1.3 and delineate its role in STAT mediated interferon signaling. For In vitro studies, we used BV2 microglia stably expressing Kv1.3 protein, containing a V5 tag as well as fused to TurboID, a biotin ligase. IFN signaling was induced by either type 1 IFN (100 u/ml,30 minutes) or type 2 IFN (10ng/ml, 30 minutes), and the role of Kv1.3 channels was assessed by blocking Kv1.3 channels prior to IFN stimulation using a small molecule blocker (PAP-1,1µM). We measured phospho- and total levels of STAT1 and STAT3 along with other IFN-signaling proteins (eg. JAKs), by Western Blot of whole-cell lysates. We found that the IFN-induced phosphorylation of both STAT1 and STAT3 were significantly reduced by Kv1.3 blockade. Interestingly, type 2 IFN exhibited stronger induction and inhibition of STAT phosphorylation compared to type 1 IFN. We further validated the physical interaction of Kv1.3 and STAT proteins and the effect of PAP-1 using V5-based co-immunoprecipitation, consistent with TurboID-based proximity labeling proteomics. While the TurboID approach captures transient and stable interactions, co-IP approaches using the V5 tag capture stable interactors of Kv1.3 channels. Based on preliminary validation of these two approaches, our ongoing proteomics studies will contrast Kv1.3 interactors identified by TurboID-based proximity labeling and V5-based co-IP to delineate and validate Kv1.3 channel interactors in microglia, under different inflammatory activation states. Together, we provide evidence that Kv1.3 channel function directly regulates IFN-mediated STAT activation, most likely via interaction at the level of IFN receptors on the cell surface, a novel mechanism for immune regulation of microglia by Kv1.3 channels. Future studies will also investigate the effect of PAP-1 on downstream targets of interferon signaling in primary cells and 5xFAD mouse models of Alzheimer’s disease.

Disclosures: R. Kumari: None. **A. Brandelli:** None. **C. Bowen:** None. **H. Wulff:** None. **S. Rangaraju:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

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Topic: F.04. Neuroimmunology and Neurovirology

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Alz Association AARG-NTF-22-974072 to NCT
Rackham Merit Fellowship to LC

Title: Oral contraceptive exposure modulates neuroimmune activity

Authors: *L. M. CONRAD[1,2], H. CHOI[3], K. M. SCHUH[1], K. LINDSAY[3], N. C. TRONSON[4]; [1]Univ. of Michigan Psychology Grad. Program, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Univ. of Michigan, Ann Arbor, MI; [4]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Hormonal contraceptives including oral contraceptives (OCs) are the most widely prescribed class of drugs in the world. OCs are typically a combination of ethinyl estradiol and a synthetic progestin and induce negative feedback to suppress endogenous ovarian hormone cycling and prevent pregnancy. Beyond reproductive effects, estradiol and progestogens modulate physiological function throughout the body and brain, including the peripheral and neuroimmune systems. In this project, we examined whether OC exposure modulates neuroimmune cells and signaling. Given the importance of neuroimmune function in risk for neurodegenerative diseases, including Alzheimer's disease (AD), we also examined whether OC-modulation of neuroimmune processes protect against pathology in AD transgenic mice. Female C57Bl/6N mice readily drank ethinyl estradiol and levonorgestrel in sucrose (EE, 0.02μg+LVNG, 0.75μg in 0.25mL 10% sucrose; vs 10% sucrose alone) given daily prior to lights out in their home cage. After treatment of EE+LVNG for one month, mice from each group were injected intraperitoneally with either a single strand RNA immune challenge (R848 in 4% DMSO and PBS;1000 μg/kg) or a vehicle injection (4% DMSO and PBS;1000 μg/kg). We used bead based multiplex cytokine assays (Luminex) to assess 15 different cytokines across prefrontal cortex, dorsal and ventral hippocampus, and hypothalamus. We found that mice treated with EE+LVNG showed significantly higher levels of CXCL10 after R848 treatment as compared to OC untreated mice, whereas IL-1β and IL-10 showed no differences between treatment groups. Across all cytokines measured, we observed a brain-region specific change in cytokine networks with OC treatment at baseline and after immune challenge. This response differed across brain regions suggesting a distinct effect of EE+LVNG and immune responses in the brain. Finally, we observed OC-modulation of neuroimmune states in 5xFAD and APP/PS1 AD model mice. Given that neuroimmune processes and hormone contraceptive use can

influence risk for later cognitive decline and AD, further research will investigate cytokine networks across brain regions to determine how OC mediated neuroimmune changes modify the development of AD.

Disclosures: L.M. Conrad: None. **H. Choi:** None. **K.M. Schuh:** None. **K. Lindsay:** None. **N.C. Tronson:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.14/D59

Topic: B.09. Glial Mechanisms

Support: KBRI Basic Research Program 24-BR-04-03

Title: Single-cell transcriptome analysis reveals that microglial activation by overexpression of GATA1 in mouse mPFC

Authors: S. SHIN, J. KWON, K. CHOI, J. LEE, *H. KANG;
Chung-Ang Univ., Seoul, Korea, Republic of

Abstract: GATA1, an essential master regulator of erythropoiesis and several hematopoietic pathways has been implicated in MDD. Conventional microarray data reported high GATA1 expression in MDD brain and subsequent studies have revealed that polymorphism at the GATA1-binding site in the promoter of IL-6 which is increased in MDD. These suggest a potential role of GATA1 modulating immune response in depression. However, a complete catalog of heterogeneous immune cell types in the mouse brain has not yet been fully elucidated. Here, we used single-cell transcriptomics to examine approximately ~80.000 cells from the whole brain of GATA1 overexpressed mice (n=4) and controls (n=4) following immune cell enrichment with percoll gradient. We identified 14 broad cell types and profiled diverse immune cell types in the mouse brain. We detected alterations of microglial subtype proportion in the GATA1 mice group, along with robust upregulation of genes related to adaptive immune response and M1 phenotype marker including Ly6c, Ctsg, Elane, Cxcl1, and Ccl7. Among the microglial subtype, IFN microglia, which expressed a higher level of interferon transcripts such as IFit3, Ifi204, and Ifitm3, showed a significantly increased proportion in the GATA1 group. In addition, overall interferon-related gene expressions were significantly upregulated in the microglia of the GATA1 group. Cell-cell interaction analysis showed increased communication between microglia and neutrophils in the brain of the GATA1 group. We present evidence of a potential link between GATA1 and microglial activation and immune activation. Collectively, this study provides a comprehensive immune cell atlas of the mouse brain and molecular foundation for investigating cell type-specific responses to overexpression of GATA1.

Disclosures: S. Shin: None. **J. Kwon:** None. **K. Choi:** None. **J. Lee:** None. **H. Kang:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.15/D60

Topic: B.09. Glial Mechanisms

Support: NSERC
CHRI

Title: Interrogating the role of the integrated stress response in microglia polarity

Authors: *E. KANE[1], N. CRUICKSHANKS[1], S. P. CREGAN[2], S. N. WHITEHEAD[3]; [1]Western Univ., London, ON, Canada; [2]Robarts Res. Inst., London, ON, Canada; [3]Anat. and Cell Biol., Univ. of Western Ontario, London, ON, Canada

Abstract: Microglia are the sentinels of the central nervous system, responsible for initiating the innate immune response when challenged by pathogens, trauma, or disease. The transient activation of microglia is key to maintaining tissue homeostasis and neuronal function. Chronic inflammation, denoted by phenotypically dystrophic microglial populations, is pervasive in numerous idiopathic age-related neurodegenerative pathologies. Dystrophic microglia display distinct intrinsic impairments in phagocytic activity, autolysosome-mediated degradation and metabolic function accompanied by sustained pro-inflammatory signalling. Microglial polarization via canonical receptor-mediated activation has been extensively characterized, however, little is understood regarding the contribution of cell-intrinsic dysfunction. The endoplasmic reticulum (ER) is a key intracellular hub, wherein reciprocal interactions with organelles such as mitochondria and lysosomes form a signalling axis sensitive to perturbations in proteostasis. The integrated stress response (ISR) is a conserved cytoprotective cascade attuned to ER-mediated signalling and cell-intrinsic dysfunction. In peripheral macrophages, ISR signalling has been attributed to non-canonical NF-kB signalling, inflammasome activation, and secretion of pro-inflammatory cytokines. Given the putative role of the ISR in mediating both intracellular homeostasis and cell-extrinsic signalling, it is an attractive target to interrogate as a novel modulator of microglia polarization. We have demonstrated *in vitro*; that toxin-mediated perturbations to proteostasis, proteolysis and metabolic function induce concomitant ISR activation and pro-inflammatory polarization of primary microglial. We observe acute expression and anterograde trafficking of pro-inflammatory markers accompanied by inflammasome activation and secretion of pro-inflammatory cytokines. Mediation of ISR activity, via small molecule inhibitors, ameliorates both the phenotypic markers of microglial reactivity and the release of pro-inflammatory cytokines. Further, ISR inhibition mitigates phenotypic indicators of dystrophia, significantly increasing microglia survival, phagocytic activity, and homeostatic morphology. Taken together, our results demonstrate a novel mechanism of microglial activation via characterized intrinsic dystrophic phenotypes, implicating inter-organelle stress signalling axes and ISR activation as a key mediator of pro-inflammatory microglia polarization.

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Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

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Program #/Poster #: PSTR455.16/E1

Topic: B.09. Glial Mechanisms

Support: NIH/Arkansas INBRE P20 GM103429

Title: Iron alters activation of cultured murine microglia and impacts regulation of inflammation-related transcription factors

Authors: J. PARKER[1], N. MCNAUGHTON[2], A. SCOTT[3], *D. DONLEY[1];
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Abstract: Free radicals drive oxidation/reduction (redox) reactions that coordinate intracellular signaling. Buildup of radicals and/or dysregulation of redox pathways causes oxidative stress that damages cells. Microglial cells are Central Nervous System resident immune cells that are sensitive to oxidative stress at both the cellular and tissue level. Inflammation is associated with this stress in microglia and their response to disease-associated stimuli such as amyloid beta. Microglial dysfunction from long-term oxidative stress is implicated in the potentiation of neurodegenerative diseases such as Alzheimer's Disease (AD) and is associated with elevated iron. However, the interaction between redox-active iron, oxidative stress, and microglial inflammation is unclear. To study this relationship, we treated cultured microglia with elevated iron and with ferrostatin, a transferrin receptor inhibitor and putative radical scavenger, with and without Aβ stimulation. This design allows use to explore the impact of elevated iron as well as its typical role in the inflammatory process. We found that ferrostatin decreases radical generation and suppresses activity of the pro-inflammatory enzyme, inducible nitric oxide synthase. Conversely, iron suppresses anti-inflammatory pathways and cytokine production resulting in a hyper-inflammatory phenotype. This indicates that ferrostatin may push microglia towards an anti-inflammatory state while elevated iron primes the cell to be hyper-activated by extrinsic stimuli. Using proteomics, we identified candidate transcription factors that are impacted by iron and/or amyloid beta. Herein we report the impact of cellular iron status on inflammation-related transcription factors. To explore the relative contribution of these transcription factors, we used siRNA to knockdown expression in the context of iron and amyloid-beta using a factorial design. The exact mechanism(s) of how iron contributes to disease-associated inflammation in microglia is unclear; however, our results indicate that iron dysregulation promotes inflammation and modulates responses to extrinsic stimuli in part by altering the response to stimuli such as amyloid beta. Future research will elucidate how iron-sensitive genes impact inflammatory responses in microglia.

Disclosures: J. Parker: None. **N. McNaughton:** None. **A. Scott:** None. **D. Donley:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

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Topic: B.09. Glial Mechanisms

Support: SURF Grant 2024
NIH/Arkansas INBRE P20 GM103429

Title: Regulation of c15orf48 controls microglial inflammation: a role for methylation?

Authors: *G. A. BING[1], B. BISHOP[2], D. DONLEY[3];
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Abstract: Accumulation of iron and beta-amyloid (Aβ42) is a hallmark of Alzheimer's Disease (AD), and they are thought to play a role in pathogenesis. Microglia are the tissue-resident immune cells of the central nervous system and have been shown to be hyper-activated in the early stages of AD. Interestingly, coincident with increased reactivity as a result of tandem treatment of iron with Aβ42 stimulation, we found that global methylation was significantly decreased in murine microglia. Methylation is a key epigenetic modification and is associated with modifying the gene expression pattern in AD. In the current study, we investigate this phenomenon using the pan-DNA methyltransferase (DNMT) inhibitor, SGI-1027, which will be used to induce hypomethylation of the genome in order to determine its impact on microglial activation. The *C15orf48* gene was identified as a putative intersection point of iron and Aβ42 and encodes the NMES1 protein and the microRNA mir-147b, both of which are associated with facilitating inflammatory responses of microglia. There is evidence of transcriptional dysregulation in AD, both globally and at the *C15orf48* locus. Upon stimulation of cultured microglial cells with beta-amyloid, we found that *C15orf48* expression increased, but the addition of iron attenuated the response. This preliminary finding identifies *C15orf48* regulation as a potential intersection point of disease-associated pathways. In cancer cells, the NMES1 gene has been found to be heavily methylated, suggesting that this may be one mechanism of regulation. Despite this, regulation of the *C15orf48* gene is not well understood. Herein, we report the impact of methylation status on regulation of *C15orf48*. It is known that methylation is a key regulator of gene expression, but more research to examine the extent to which it controls *C15orf48* expression in microglia is necessary. This work will provide insight on the significance of *C15orf48* in directing inflammatory responses of microglia.

Disclosures: G.A. Bing: None. **B. Bishop:** None. **D. Donley:** A. Employment/Salary (full or part-time):; Harding University.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

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Program #/Poster #: PSTR455.18/E3

Topic: B.09. Glial Mechanisms

Support: PID2019-110721RB-I00

Title: Rna binding protein imp1/zbp1 drives mrna localization and local translation in microglial peripheral processes and mediates morphological changes, motility and phagocytosis in response to inflammation

Authors: *J. IMAZ-IRURETAGOYENA[1,2], M. MÁRQUEZ[1,2], A. SIERRA[4,3,5], J. BALERIOLA[1], J. BALERIOLA[1,5];
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Abstract: Central Nervous System cells exhibit significant diversity and specialization, not only between cell types and functions, but also regarding their morphology. Such morphological and functional polarization complexity is due to the uneven distribution of proteins at a subcellular level. This distribution can be obtained either by protein transport to a specific cell site, or by mRNA transport creating a site-specific transcriptome that can be translated in a stimulus dependent manner, allowing cells to react to environmental changes. This last mechanism is called local protein synthesis or local translation and has been long known to happen in neurons. However, evidence suggests that oligodendrocytes, astrocytes, and radial glia also rely on local translation to maintain protein homeostasis and functional integrity. Local translation in microglia has been observed, but its specific relationship to pathology remains unclear. Given the scant evidence, our study aims to investigate the existence of local translation in microglial peripheral processes (PeMPs) and unravel its functional significance in response to inflammation. Using primary microglia cultures and bacterial lipopolysaccharides (LPS), we have seen that Actb mRNA polarizes to PeMPs and is locally translated upon LPS exposure. Interestingly, downregulation of the Actb binding protein IMP1/ZBP1 impaires Actb mRNA polarization and its localized translation, and leads to defects in filopodia distribution, PeMP motility, directed migration and phagocytosis in microglia. In an *in vivo* study, we conducted immunohistochemical and *in situ* hybridization analyses following intraperitoneal LPS injections in 1mo mice. Results suggest that LPS enhances local protein synthesis *in vivo*, as phosphorylation levels of ribosomal protein Rsp6 increase in cortical PeMPs. We analyzed *Actb* mRNA levels in mice and observed an increase in cortical growth cone (GC)-like PeMPs and in phagocytic pouches in the dentate gyrus in response to LPS. Interestingly, IMP1 expression increases in primary PeMPs in the cortex and in phagocytic pouches in response to LPS. Indeed, we observed a significant positive correlation between *Actb* and IMP1 in phagocytic microglia suggesting IMP1 drives *Actb* localization *in vivo*. Altogether, our study confirms local translation in PeMPs and thath it is enhanced in microglial inflammatory response with LPS suggesting a functional relevance of this molecular mechanism in response to inflammation. This adds to the

evidence supporting mRNA localization and localized translation in microglia, offering mechanistic insights into their crucial role in responding to inflammation.

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Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.19/E4

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

Title: Validation os a Systems Biology Platform for Neuroinflammation with Benchmark Pharmacological Agents

Authors: L. AGHOLME[1], A. SKILJE[1], C. NODIN[1], B. MA[2], M. KARLSSON[1], *J. PIHL[1], J. M. LEVENSON[2];
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Abstract: Dysfunction of microglia has been linked to a variety of CNS disorders including neurodegenerative, neuropsychiatric, and optic neuropathy. We developed a neuroinflammatory screening platform that integrates human IPSC-derived microglia into rodent primary neuron-astrocyte co-cultures. This platform is cost-effective and enables medium-throughput screening of compounds for a variety of activities relevant to neuroinflammation and microglial biology. Using a variety of technologies, a number of imaging endpoints have been qualified for screening including MAP-2 neuronal morphology, GFAP astrocyte morphology, and IBA-1 microglial morphology. Multiplexed analysis of pro-inflammatory cytokine levels in conditioned media is also qualified. Using commercially available compounds, the role of 10 different targets implicated in neuroinflammatory responses was characterized. Our results show differential activity of many targets on microglial-mediated cytokine release and microglial morphology, where many compounds suppress cytokine release but fail to shift microglia back into a morphological state characteristic of neuroprotection. Application of machine learning to diverse screening data has enabled creation of a multi-component screening score that identifies several classes of compounds with distinct effects on microglial functional state. Collectively, these results support utilization of a screening workflow that incorporates multiple orthogonal endpoints of microglial functional state to fully characterize pharmacology of compounds of interest.

Disclosures: L. Agholme: A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Skilje:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C. Nodin:** A. Employment/Salary (full or part-time):; Cellectricon AB. **B. Ma:** A. Employment/Salary (full or part-time):; FireCyte Therapeutics, Inc. **M. Karlsson:** A. Employment/Salary (full or part-time):;

Cellectricon AB. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB. **J.M. Levenson:** A. Employment/Salary (full or part-time):; FireCyte Therapeutics, Inc..

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.20/E5

Topic: B.09. Glial Mechanisms

Support: NS112706

Title: The role of ATP synthase c-subunit leak channel in neuroinflammation

Authors: *J. CHEN[1], P. LICZNERSKI[2], R. CHEN[3], E. A. JONAS[4];
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Abstract: Neuroinflammation induced by lipopolysaccharide (LPS) has been associated with memory impairments and behavioral disorders. Microglia, as the primary immune cells in the brain, orchestrate the inflammatory microenvironment. During neuroinflammatory conditions, microglia undergo metabolic reprogramming, shifting their main metabolic pathway from oxidative phosphorylation to aerobic glycolysis. Our prior research identified the ATP synthase c-subunit as a key player in this glycolytic reprogramming. In our current study, we discovered the formation of a mitochondrial inner membrane leak facilitated by the ATP synthase c-subunit during LPS stimulation in microglia. Inhibition of this leak channel activity reduced pro-inflammatory cytokine production, while overexpression exacerbated the inflammatory response. We hypothesize that the ATP synthase c-subunit leak channel regulates inflammation by modulating metabolic shift. To elucidate this relationship, we employed mass spectrometry to analyze the proteome change of microglia under conditions of leak channel overexpression and inhibition. Our data provide insights into the potential therapeutic targeting of ATP synthase c-subunit leak channel in neuroinflammation.

Disclosures: J. Chen: None. **P. Licznerski:** None. **R. Chen:** None. **E.A. Jonas:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.21/E6

Topic: B.07. Network Interactions

Support: R_PRIN_2022_NEUR

Title: Spinal cord neuronal and glial responses to pro-inflammatory small extracellular vesicles

Authors: *L. RECUPERO[1], M. PACHETTI[1], R. AMORIELLO[2], F. DE CASTRO REIS[1], C. BALLERINI[2], L. BALLERINI[1];
[1]Neurobio., SISSA, Trieste, Italy; [2]Dept. of Exptl. and Clin. Med., Univ. of Florence, Florence, Italy

Abstract: Central Nervous System (CNS) small Extracellular Vesicles (sEVs) are nanostructured membranous particles released by virtually any cell phenotype to mediate intercellular communication in multiple physiological as well as pathological processes. In the CNS, sEVs release might impact neuroinflammation spreading to healthy nervous tissue, reinforcing pathological inflammation loops. We used mouse (E12) organotypic spinal cord (SC) explants (in their 3rd week *in vitro*) to isolate sEVs, from control slices and from slices exposed for 4h to a pro-inflammatory cytokines cocktail (CKs: IL-1β, GM-CSF and TNF-α), a treatment known to induce mild neuroinflammatory CNS reactivity (Giacco et al., 2019). Upon successful separation of sEVs, achieved via ultracentrifugation and size-exclusion chromatography, further validated via Western Blot for EVs markers (GM130-, TSG101+, CD63+, FLO1+), we addressed the role of sEVs isolated in inflammatory conditions ($sEVs_{ck}$) in spreading reactivity in naïve slices exposed to $sEVs_{ck}$ for 4h or 24h. By single neuron whole-cell voltage clamp we measured ventral interneuron glutamatergic bursting activity, significantly increased by exposure to $sEVs_{ck}$. Immunofluorescence and confocal microscopy of the same SC cultures detected a significant increase in ameboid morphology of IBA1+ microglia, supportive of reactive states. By live calcium imaging, performed via AAV5:gfaABC1D-cyto-GCaMP6f, we selectively monitored calcium dynamics in astrocytes. In naïve slices exposed to $sEVs_{ck}$ the frequency of intracellular calcium oscillations was significantly increased, with a decrease in event synchronization, both features usually associated with a reactive phenotype. Simultaneous patch clamping and calcium dynamic recordings, from neurons and astrocytes, respectively, supported a lack of temporal correlation between the two signals, in control and upon $sEVs_{ck}$ treatment. Such finding implies that pro-inflammatory vesicles did not influence neuron-astrocyte interplay, despite effectively altering both populations. Altogether, our results provide valuable insights on the ability of CNS-derived sEVs to act as carriers of information in an etio-pathological context, exploring their wide range of effects in a complex tissue model, which was not extensively studied so far. References Giacco V, Panattoni G, Medelin M, Bonechi E, Aldinucci A, Ballerini C, Ballerini L. Cytokine inflammatory threat, but not LPS one, shortens GABAergic synaptic currents in the mouse spinal cord organotypic cultures. J Neuroinflammation. 2019 Jun 25;16(1):127. doi: 10.1186/s12974-019-1519-z.

Disclosures: L. Recupero: None. **M. Pachetti:** None. **R. Amoriello:** None. **F. de Castro Reis:** None. **C. Ballerini:** None. **L. Ballerini:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.22/E7

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

Support: PHS Grant R01DA045063

Title: Individual differences in neuroimmune states in a model of addiction-vulnerability

Authors: *H. CARMON[1], T. CABALLERO[2], J. EMERSON[3], M. SARTER[4], N. C. TRONSON[5];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Neurosci., University of Michigan, Ann Arbor, MI; [3]Neurosci. Dept., Univ. of Michigan, Ann Arbor, MI; [4]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI; [5]Dept. of Psychology, Univ. of Mchigan, Ann Arbor, MI

Abstract: Sign-tracking (ST) rats attribute incentive salience toward reward cues and exhibit poor attentional performance, compared to their goal-tracker (GTs) counterparts. These attentional deficits are associated with dysfunctional intracellular choline transporters (CHTs) that, in turn are associated with elevated neuroimmune function. Whereas STs have higher cytokine levels and CHT dysfunction than GTs in prefrontal cortex at baseline, only GTs show robust increase in cytokine levels and CHT ubiquitination after a lipopolysaccharide (LPS) challenge. Here we investigated the hypothesis that the attentional deficits in STs are caused by microglia activation and higher cytokine levels at baseline compared to GTs. We anticipate that GTs are more vulnerable to the impact of immune challenge, whereas STs are resilient to further neuroimmune activation. Prior to an immune challenge, cytokine levels measured in the frontal cortex and striatum were higher in STs than in GTs. Across almost all cytokines, only GTs showed increased levels following LPS. We used qPCR to measure microglia and astrocyte activation states, refining neuroimmune ST/GT differences. *Spalt-like transcription Factor 1* (*Sall1*) is inversely related to microglia activation, where low *Sall1* indicates increased microglia activity. STs express lower levels of *Sall1* in the frontal cortex compared to that of GTs. Consistent with this finding - and elevated cytokine levels - STs also showed higher levels of microglia activity markers (*Iba1, CD45,* and *CD11b*). After LPS, and consistent with our cytokine data, GTs showed the expected increase in *Iba1, CD45,* and *CD11b,* and reduced *Sall1* expression whereas STs did not. Data on astrocyte markers suggests a more complex story. We observed no differences between STs and GTs in baseline astrocyte activity markers *(GBP2 and LCN2)* but in contrast to microglia data, a stronger increase after the immune challenge in STs compared with GTs. Additional studies demonstrate the relationships between microglia activity, sign-tracking, and attentional function. Together, these data reinforce the critical role of complex neuroimmune activity in behavioral phenotypes and addiction vulnerability traits, including that indexed by sign-tracking.

Disclosures: H. Carmon: None. **T. Caballero:** None. **J. Emerson:** None. **M. Sarter:** None. **N.C. Tronson:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.23/E8

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

Support: NIH Grant 1R35NS132349-01

Title: Regulation of microglial reactivity and inflammation-induced depression-like behaviors by Orai1 calcium channels

Authors: *K. DEMEULENAERE[1], M. E. MARTIN[1], M. YAMASHITA[2], M. PRAKRIYA[3]; [1]Northwestern Univ., Chicago, IL; [2]Northwestern Univ. Med. Sch., Chicago, IL; [3]Pharmacol., Northwestern Univ. - Chicago, Chicago, IL

Abstract: Store-operated Orai1 channels are implicated in triggering inflammatory responses in immune cells and regulate a wide range of cellular effector functions, including gene expression, metabolism, and proliferation. Microglia are the primary immune cells in the central nervous system and play a key role in mediating inflammatory responses in the brain that lead to depression and anxiety. However, the molecular checkpoints controlling cell state changes of microglia from homeostatic to inflammatory microglia are not well understood. Here, we investigated the role of Orai1 calcium channels in regulating microglia-mediated neuroinflammation in an LPS-induced depression model. Conditional deletion of Orai1 in microglia abolished store-operated calcium entry (SOCE) and reduced G-protein coupled receptor (GPCR)-mediated Ca^{2+} signals in hippocampal microglia. We evaluated microglia activation in vivo and neuroinflammatory markers in the brain in response to peripheral administration of lipopolysaccharide (LPS). Gene expression analysis indicated that conditional deletion of Orai1 in microglia reduced levels of inflammatory cytokines, including IL-6, IL-1β, and TNFα, in the hippocampus 48 hours after intraperitoneal injection of LPS (1mg/kg). Additionally, deletion of Orai1 in microglia led to reduced expression of reactive microglia and astrocyte markers including IBA1 and GFAP in mice at both 24 and 48 hours after peripheral LPS administration. Consistent with these changes in neuroinflammation and glia reactivity, conditional Orai1 microglia KO mice showed significant protection from developing inflammation-induced depression-like behaviors including anhedonia and helplessness. Taken together, these results show that Orai1-mediated Ca^{2+} signaling plays an essential role in stimulating microglial reactivity to cause multi-level inflammatory changes in the brain that underlie the development of depression-like behaviors.

Disclosures: K. DeMeulenaere: None. **M.E. Martin:** None. **M. Yamashita:** None. **M. Prakriya:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.24/E9

Topic: B.09. Glial Mechanisms

Title: Exploring the role of microglia in CNS Lupus Pathogenesis in vivo

Authors: *M. SHINDO[1], H. WAKE[2];
[1]Nagoya Univ., Nagoya city , Aichi prefecture, Japan; [2]Dept. of Anat. and Mol. Cell Biol., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan

Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease caused by activation of Toll-like receptor (TLR) 7 signaling in innate immune cells and subsequent CD4+ T cell-dependent immune responses. Interestingly, the central nervous system lupus (CNS lupus) has been known despite the absence of T cells in the physiological state in CNS. Here, we clarified that microglial activation is involved in T cell infiltration into the brain parenchyma using continuous intravital imaging and transcriptome analysis of microglia in SLE mouse models. The TLR7 agonist, Imiquimod, was administered from ear skin to develop SLE in mice. Mice continuously treated with Imiquimod for 14 weeks exhibited elevated anti-dsDNA antibody levels, thrombocytopenia, and met the diagnostic criteria (EULAR) for SLE. *In vivo* imaging and immunohistochemical analyses on microglia in SLE models visualized increased microglial migration and gradually increased number of vessel-associated microglia associated with disease progression. RNA sequencing analysis of microglia in SLE models annotated significantly enriched expression of chemokines associated with T cell migration, *Ccl5*, *Cxcl10*, *Ccl12* compared to microglia in control mice. In addition, immunohistochemistry and flow cytometry of the brain cortex in SLE models revealed significant T cell infiltration into the brain cortex. These observations suggest that SLE is associated with a microglial response expressing specific chemokines and with T cell infiltration into the brain parenchyma. Currently, we are investigating the specific roles of candidate chemokines by their inhibition, and the necessity of microglia for the development of T cell infiltration using microglia specific ablation. Furthermore, we will explore the molecular characteristics of disease-specific microglial subsets for SLE by single cell analysis and visualize these to determine the therapeutic target cells in SLE.

Disclosures: M. Shindo: None. **H. Wake:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.25/E10

Topic: B.09. Glial Mechanisms

Support: NIH/Arkansas INBRE

Title: Iron suppresses the microRNA, mir-147b and the NMES1 protein in cultured mouse microglia, potentiating inflammation in response to beta-amyloid in vitro

Authors: *B. BISHOP[1], T. SANDERS[2], S. EWING[3], J. SINZI[4], D. DONLEY[5];
[1]Harding, Searcy, AR; [2]Harding Univ., Burleson, TX; [3]Biol., Harding Univ., Searcy, AR;
[4]Harding Univ., kigali, Rwanda; [5]Harding Univ., Searcy, AR

Abstract: Iron dysregulation in microglia cells promotes dystrophy and modulates activation in response to disease stimuli such as beta-amyloid. Accumulation of beta-amyloid results in chronic microglia activation linked with the progression of Alzheimer's disease (AD). In addition, the buildup of iron is associated with AD progression, and preliminary data finds that iron potentiates microglial activation in response to beta-amyloid. The mechanism(s) of how elevated iron and beta-amyloid converge to induce microglia dysfunction is unclear. To study this intersection, murine microglia were cultured in iron then treated with/without beta-amyloid in a factorial design. We completed a proteomic analysis to identify potential intersection points of beta-amyloid and iron. Normal mucosa of esophagus-specific gene 1 (NMES1) was the sole protein altered in all three experimental groups. The host gene for the NMES1 protein is C15orf48, and it also produces the microRNA mir-147b. NMES1 is a subunit of mitochondrial cytochrome c oxidase and an inflammatory regulator. Our data suggest that iron attenuates the ability of C15orf48 gene products to regulate microglial activation. Based on the literature and preliminary data, we hypothesize that NMES1 and mir-147b may be critical mediators of inflammation that are affected by iron. To study this, we transfected cultured microglia with a mir-147b inhibitor and NMES1 siRNA. We found that inhibition of this microRNA and protein potentiates the inflammatory response of microglia to beta-amyloid, thereby supporting its role as an inflammatory regulator. Herein, we report on the role of mir-147b and NMES1 in regulating oxidative stress and mitochondrial metabolism - which have both been suggested as potentiators of inflammation in AD. More research is needed to fully elucidate the role of C15orf48 and its gene products on microglial activation and to determine the mechanism by which iron alters expression of this gene. Our data expands on the current understanding of the mechanisms underlying microglial activation states and suggests that iron dysregulation in microglia may be impairing important inflammatory regulators, such as mir-147b and NMES1, in the context of beta-amyloid activation.

Disclosures: B. Bishop: None. **T. Sanders:** None. **S. Ewing:** None. **J. sinzi:** None. **D. Donley:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.26/E11

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

Title: Calcium Modulation Attenuates Neuroinflammation in LPS-Stimulated BV2 Microglial Cells

Authors: *A. MAJID[1], M. SALMAN[2], T. ISHRAT[2], D. LEBECHE[3];
[1]Dept. of Physiol., [2]Dept. of Anat. and Neurobio., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [3]Dept. of Physiol., The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Microglia, the primary immune cells in the central nervous system, play acrucial role in preserving homeostasis and combating insults.Dysfunctions in microglial activity, particularly in neuroinflammatory milieus,underscore the urgency to unravel their intricate signaling mechanisms associatedwith the onset and progression of neurological conditions. Calcium signalingemerges as a key orchestrator in microglial activation and the modulation ofneuroinflammatory cascades. This interplay between neuroinflammation andcalcium dynamics illuminates the multifaceted mechanisms underpinning thepathophysiology of neurological disorders, emphasizing the potential forcalcium signaling as a therapeutic avenue to mitigate neuroinflammatoryresponses and associated neuronal damage. This study aims to examine theeffects of a calcium-modulating compound (CMC) on BV2 microglial cells and elucidateits anti-inflammatory mechanisms under lipopolysaccharide (LPS)-inducedconditions. We show that CMC significantly limits LPS-triggered proliferationand activation of BV2 microglial cells *in-vitro* and shifts theirphenotype from a pro-inflammatory M1 to an anti-inflammatory M2 state.Furthermore, CMC reduces the release of pro-inflammatory cytokines andattenuates the expression of inflammatory markers, including calcium-regulatedand OXPHOS proteins. Wound healing migration assays demonstrate the ability ofCMC to mitigate LPS-induced BV2 cell migration. Additionally, the decline inmitochondrial respiration following LPS exposure was counteracted by CMCtreatment. Altogether, these findings underscore the potential of CMC insuppressing neuroinflammation in BV2 microglial cells through the regulation ofcalcium dynamics. The elucidation of these intricate mechanisms not onlyprovides valuable insights into potential therapeutic targets forneuroinflammatory disorders but also holds promise for the development of novelinterventions to combat neurological conditions.

Disclosures: A. Majid: None. **M. Salman:** None. **T. Ishrat:** None. **D. Lebeche:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.27/E12

Topic: B.09. Glial Mechanisms

Support: UROP Individual Grant Summer, 2024
UROP TEAMS Grant Summer, 2024
UROP TEAMS Grant Academic Year, 2024-25

Title: Time course analysis of the effects of M. vaccae NCTC 11659 on gene expression in naïve or lipopolysaccharide-challenged BV2 microglial cells

Authors: *I. RUTHERFORD[1], C. A. LOWRY[2], X. CISNEROS[1], E. COLE[3];
[1]Mol. Cell. Developmental Biol., [2]Integrative Physiol., [3]Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: Previous studies have shown that immunoregulatory bacteria with anti-inflammatory and immunoregulatory properties such as *Mycobacterium vaccae* NCTC 11659 can promote stress resilience in rodent models. A recent study showed that exposure of a murine BV2 microglial cell line to whole, heat-killed *M. vaccae* NCTC 11659 (100 μg/mL), relative to vehicle conditions, and subsequent inflammatory challenge with lipopolysaccharide (LPS) exposure (250 ng/mL), relative to vehicle conditions, induces a strong adjuvant-like effect when exposure of BV2 microglial cells to *M. vaccae* NCTC 11659 precedes exposure to LPS by 24 h and mRNA expression is assessed 24 h following LPS or vehicle exposure. While *M. vaccae* NCTC 11659 exposure by itself produced the expected adjuvant-like effects, with small-fold increase in several inflammatory genes, *M. vaccae* exposure followed by LPS challenge resulted in an atypical microglial phenotype, with attenuation of LPS-induced decreases of M2 marker *Arg1*, but, paradoxically, increased expression of several key proinflammatory genes. However, one potential shortcoming with this experiment was the timing of *M. vaccae* NCTC 11659 relative to LPS exposure. Studies show that, even in vivo, *M. vaccae* NCTC 11659 induces a pronounced proinflammatory response within 12-72 h followed by anti-inflammatory and immunoregulatory responses that are long lasting, with maximal responses 4-6 weeks after exposure. Though previous work has made promising suggestions regarding the mechanism of action, the exact mechanism by which *M. vaccae* NCTC 11659 imparts its anti-inflammatory effects in BV2 cells remains unclear, and it remains possible that anti-inflammatory reprogramming takes more time than was allowed in previous studies. Thus, this experiment will analyze the effects of *M. vaccae* NCTC 11659 on BV2 murine microglial cells in a time-course manner, using intervals of 24 h, 72 h, and 168 h between *M. vaccae* NCTC 11659 and LPS exposures.

Disclosures: I. Rutherford: None. **C.A. Lowry:** None. **X. Cisneros:** None. **E. Cole:** None.

Poster

PSTR455: Microglia and Neuroinflammatory Mechanisms in CNS Disease and Injury

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR455.28/E13

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

Support: NIH Grant R03AG087482
NIH Grant R21CA274620
Mary Kay Ash Foundation Grant for Cancer Research
NIH Grant P30CA138292
NIH Grant P50CA217691
NIH Grant U54AG065187

Title: Targeting p38/MK2 protein-protein interaction to control neuroinflammation in Alzheimer's disease

Authors: A. LI, M. HU, H. FU, Y. DU, *A. A. IVANOV;
Pharmacol. and Chem. Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, and chronic neuroinflammation is one of the core AD hallmarks. Extensive *in vitro*, *in vivo*, and clinical studies have established two protein kinases - p38 and MK2 - as the key drivers of neuroinflammation in AD. Among four known p38 isoforms - α, β, γ, and δ - p38α and p38δ are ubiquitously expressed in most tissues, including the brain, and are primarily responsible for regulating inflammation. In response to stress stimuli, p38 phosphorylates and activates MAPK-activated protein kinase 2 (MK2), coded by the MAPKAPK2 gene, which regulates inflammatory cytokines, including tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and IL-6. While many p38 and MK2 inhibitors have advanced to clinical trials, none have been approved as a drug, mainly due to i) limited selectivity against other kinases and ii) a wide range of p38 substrates affected by the p38 kinase activity inhibition. The clinical failure of p38 and MK2 kinase inhibitors highlights the urgent need for novel approaches to regulate p38/MK2-dependent neuroinflammation. To address this unmet medical need, we develop a novel approach to control the p38 pathway by selectively targeting p38/MK2 protein-protein interaction (PPI) rather than p38 or MK2 kinase activity. Our Time-Resolved Fluorescence Energy Transfer (TR-FRET) and affinity pulldown assays revealed that MK2 has a significantly higher binding affinity to p38α and p38β than to p38γ and p38δ isoforms. Through the computational modeling, we identified high-affinity binding pockets on the p38α/MK2 interface, design short inhibitory peptides, and conducted virtual screening of small molecule p38/MK2 PPI inhibitors. The experimental validation of computationally discovered hits confirmed their p38/MK2 PPI inhibitory activity at low micro-molar range in vitro and in cell lysates. The identified compounds disrupted the p38/MK2 PPI in the human microglial cells (HMC3), suppressing the oxidative stress-induced MK2 phosphorylation. To discover new potent p38/MK2 PPI inhibitors with improved pharmacological profiles, we have further optimized and miniaturized the TR-FRET assay to monitor p38α/MK2 and p38β/MK2 PPIs in the high-throughput screening (HTS) 384- and ultra-HTS 1,536-well plate formats with >20 signal/background ratio stable for >48 hours and tolerated >10% DMSO. Our data show the p38/MK2 PPI druggability, provide the first chemical tools to disrupt this pathogenic complex, and establish a new robust integrative HTS and computational platform to discover small molecule p38/MK2 PPI inhibitors to facilitate therapeutic discovery in AD and other neurological diseases.

Disclosures: A. Li: None. **M. Hu:** None. **H. Fu:** None. **Y. Du:** None. **A.A. Ivanov:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.01/E14

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

Support: JSPS KAKENHI 22K09092

Title: Administration of beta2-adrenergic receptor agonists reduces allodynia in a mouse model of neuropathic pain.

Authors: *C. TSUBOI, Y. NOMURA, S. MIZOBUCHI;
Kobe Univ., Kobe/Hyogo, Japan

Abstract: Introduction: The anti-allodynic effects of β2-adrenoceptor agonists on mouse models of neuropathic pain have been studied. However, the mechanisms underlying these effects are still unclear. This study aimed to investigate the effects of β2-adrenoceptor agonists on the sciatic nerve and dorsal root ganglia (DRG) of a mouse model of neuropathic pain. Methods: C57/BL6J mice (8-10 weeks old, male, n=5-18/group) were used to create a Spared Nerve Injury (SNI) model of neuropathic pain. Intraperitoneally administered clenbuterol(a β2 adrenergic receptor agonist; the CLEB group) was compared with intraperitoneally normal saline(the NS group). The medications were given 6 days before surgery for 13 consecutive days (pre-intervention) or 14 days after surgery for 14 consecutive days (post-intervention). The von Frey test was used to assess mechanical allodynia. Sciatic nerve and DRG were surgically collected after the end of drug administration. Samples were subjected to immunohistochemical staining to determine the extent of macrophage infiltration. In addition, gene expression of inflammatory and anti-inflammatory factors was analyzed using qPCR. Statistical analysis was performed using the Mann-Whitney U test, with $p<0.05$ indicating a significant difference. Results: In the pre-intervention model, the CLEB group exhibited significant improvement in pain threshold from postoperative day 2 (8 days after drug administration). Immunological staining showed a significant decrease in DRG macrophages in the CLEB group. qPCR analysis showed that inflammatory cytokines (IL-1β and TNFα) in the DRG and sciatic nerve were reduced in the CLEB group. On the other hand, in the post-operative intervention model, the CLEB group displayed significant improvement in pain thresholds starting on postoperative day 21 (7 days after drug administration). Furthermore, the postoperative intervention model showed a trend towards increased expression of an anti-inflammatory factor (Arg-1) in the sciatic nerve and DRG. Conclusions: Clenbuterol administration significantly alleviated neuropathic pain. It also affected the expression of inflammatory and anti-inflammatory factors in the sciatic nerve and DRG. In a preoperative intervention model, clenbuterol administration reduced macrophage infiltration of the DRG. Reduction in the inflammatory response in the DRG may be linked to reduced macrophage infiltration of the DRG.

Disclosures: C. Tsuboi: None. **Y. Nomura:** None. **S. Mizobuchi:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.02/E15

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

Title: Impacts of anti-AQP4 monoclonal antibodies on localizations of AQP4 and its associated proteins in murine brain tissue: early molecular events in neuromyelitis optica spectrum disorder (NMOSD) pathogenesis

Authors: *Y. YOSHIKAWA, Y. ABE, M. YASUI, M. NURIYA;
Pharmacol., Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: Neuromyelitis optica spectrum disorder (NMOSD) is characterized by the autoimmune antibodies against aquaporin 4 (AQP4). Because NMOSD generally undergoes relapsing episodes, leading to irreversible and severe neurological damage, understanding the initial molecular changes upon anti-AQP4 antibody stimulation is crucial for designing early intervention of the disease. Currently, however, little is known about the early phase of antibodies' effects in brain tissues where specialized AQP4 localization is preserved. Here, using acutely prepared mouse brain slices, we investigated the initial molecular impacts of NMO model antibodies on AQP4 and its associated proteins. We employed two NMO model antibodies (Kurosawa et al.2015, Chen et al.2020), E5415A and E5415B; E5415A recognizes both M1 and M23 isoforms, while E5415B exclusively binds to a square array forming M23. We introduced these antibodies to wild-type C57BL/6J mouse brain tissue in vitro and observed the changes over time. We found that E5415A stimulation disrupts the uniform perivascular localization of AQP4, leading to fragmentation. Interestingly, however, this effect was not observed with E5415B. For quantlitative analysis, we performed particle analysis using the tissues 2 hours after AQP4 administration co-stained with lectin, a vessel marker. The results showed a significant increase in the ratio of AQP4 particle numbers over lectin in the ROI around blood vessels in the E5415A group compared to E5415B. This suggests that AQP4 fragmentation occurs at astrocyte endfeet by naturally occurring anti-AQP4 antibodies in NMOSD. We further addressed the potential impact of these changes on AQP4-associated proteins, because AQP4 is considered to be localized at endfeet by associating with other proteins. We found that even after AQP4 fragmentation, the high co-localization between AQP4 and dystrophin-glycoprotein complex (DGC) components such as β-dystroglycan (βDG) and syntrophin was preserved. Through quantitative analysis, we showed that there were no significant changes in the Pearson's R values of βDG or syntrophin with AQP4 between E5415A and E5415B group, in the ROI around blood vessels. This suggests that AQP4 and DGC form a cohesive complex at endfeet and antibody's binding to AQP4 affects the whole DGC complex. In conclusion, our results reveal initial molecular changes of AQP4 and associated proteins at astrocytic endfeet upon NMO model antibodies that reflect early pathological changes occurring in the NMOSD. Given the pathological significance of AQP4 disarrangement in NMO, these findings would contribute to new therapeutic strategies in the future.

Disclosures: Y. Yoshikawa: None. **Y. Abe:** None. **M. Yasui:** None. **M. Nuriya:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.03/E16

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

Title: Lrrc8a modulates t cell-mediated inflammation in the central nervous system in a mouse model of multiple sclerosis

Authors: S. YANUSHKEVICH[1], *A. ARIAS-CAVIERES[2], A. CONCEPCION[1];
[1]Biochem. and Mol. Biol., [2]Univ. of Chicago, Chicago, IL

Abstract: The volume-regulated anion channel (VRAC) is a hetero-hexameric complex formed by the protein paralogs LRRC8A-E. VRACs play a crucial role in volume regulation by releasing chloride upon hypotonic cell swelling. LRRC8A is the essential subunit of VRACs but it must combine with other paralogs to constitute functional channels. Previously, we have shown that LRRC8C$^{-/-}$ mice exacerbated experimental autoimmune encephalomyelitis (EAE) upon myelin oligodendrocyte glycoprotein (MOG_{35-55}) immunization. Here, we generated T-cell conditional knockout mice of LRRC8A to study the non-redundant role of LRRC8A in T-cells and to assess their cell-intrinsic function in the development of EAE. We show that *Lrrc8a*$^{-/-}$ $CD4^+$ T- cells lack VRAC function and displayed enhanced proliferation and survival upon activation. Moreover, *Lrrc8a* deficiency in T-cells exacerbated EAE in mice upon immunization with MOG_{35-55}. The enhanced EAE observed in *Lrrc8a*$^{fl/fl}$*Cd4*$^{Cre+}$ mice was associated with an increment in MOG-specific $CD4^+$ T-cells infiltrating the spinal cord, and production of pro-inflammatory cytokines. Overall, these findings suggest that LRRC8A play a non-redundant role in preserving T cell homeostasis against self-antigens as its deletion enhances EAE in mice.

Disclosures: S. Yanushkevich: None. **A. Arias-Cavieres:** None. **A. Concepcion:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.04/E17

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

Support: MDARC/Pepper Center/MICHR pilot funds to NCT
NIH NIA R21AG08168501
Alzheimer's Association AARG-NTF-22-974072

Title: Covid-like immune challenge as a risk for Alzheimer's disease and cognitive decline

Authors: *H. CHOI, H. WHITE, P. KE-LIND, N. C. TRONSON;
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Abstract: More than 770 million individuals globally have been infected with COVID-19, with approximately 40% of survivors experiencing long-term sequelae known as post-acute COVID sequelae (PASC or "long COVID"). Symptoms of PASC include "brain fog", cognitive

impairments, and mood-related symptoms such as depression and anxiety. Since direct infection of the brain by the SARS-CoV-2 virus is rare, non-infectious mechanisms such as inflammation, might contribute to these neurological and cognitive changes. In this project, we hypothesized that a COVID-like inflammatory event induces lasting changes in neuroimmune function, thereby potentially increase the risk for age-related cognitive decline and dementias including Alzheimer's disease (AD). Microglia, the specialized immune cells of central nervous system, alongside immune molecules such as cytokines, play crucial regulatory roles in both normal and pathological brain, including neuroplasticity, memory, and neurodegeneration. Single-stranded RNA (ssRNA) viruses, including SARS-COV2, activates innate immune responses *via* Toll-like receptors TLR7 and TLR8. Specifically, TLR7 has been implicated in cognitive impairments and neurodegenerative disorders such AD. Building on previous work that demonstrated the effects of a peripheral immune challenge on memory can persist for months after the resolution of the inflammatory response, we used a two-week subchronic immune challenge protocol with TLR7 agonist R848 (400-1000μg/kg) to identify the time course of cytokine responses and microglia changes after R848. Eight weeks after subchronic immune challenge, when memory deficits are evident, there was no overt immune activation in the periphery or hippocampus. Nevertheless, we observed male-specific elevations in microglia number and reactivity at this timepoint. These data suggest that mild-moderate transient illnesses, such as COVID-19, can trigger sex-specific and long-lasting changes in neuroimmune processes. Ongoing work is examining the role of altered neuroimmune responses in the progression and exacerbation of AD and cognitive decline following an illness.

Disclosures: H. Choi: None. **H. White:** None. **P. Ke-Lind:** None. **N.C. Tronson:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.05/E18

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

Support: FONDECYT Post-doctoral grant N 3230227 (MFG)
CONICYT-FONDAP [15130011]
FONDAP Continuation project [1523A0008]
ANID-FONDECYT- Regular [1210644] (AFGQ)
ANID-FONDECYT-Regular [1200836, 1240888] (LL)

Title: Helicobacter pylori outer membrane vesicles promote NF-kB activation mediated by TLR2 in astrocytes

Authors: *M. F. GONZALEZ CASTRO[1,2], A. F. G. QUEST[1,2], L. LEYTON[1,2];
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Abstract: *Helicobacter pylori* (*Hp*) is a gram-negative bacterium and extremely prevalent pathogen whose presence is associated with several gastric diseases. Interestingly, infection with *Hp* has also been found to correlate with several extra-gastric pathologies, including neurodegenerative conditions. The mechanisms by which *Hp* can induce or exacerbate extra-gastric diseases, appear to be related to the release of nanovesicles from the outer membrane of *Hp*, referred to as Outer Membrane Vesicles (*Hp*-OMVs). These *Hp*-OMVs are known to enter the circulatory system and reach different tissues, including the brain, where they may promote the development of neurological disorders. In astrocytes, *Hp*-OMVs induced reactivity, as evidenced by increased reactivity markers, and elevated NF-κB activation. However, the specific mechanisms by which *Hp*-OMVs exert these effects are just beginning to be understood. Available evidence suggests that Toll-like receptor 2 (TLR2) may be relevant in this context. Here, we isolated OMVs from *Hp* cultures and characterized them by Nano Tracking Analysis (NTA) and Western blotting. The size of the *Hp*-OMVs ranged from 100-150 nm (mean 128.3 +/- 14.4) and were positive for CagA, VacA and urease. The treatment of astrocytes with *Hp*-OMVs increased the phosphorylation of (pS536p65) NF-κB (two-fold) and NF-κB (p65) translocation to the nucleus (six times). Furthermore, when astrocytes were pre-treated with a blocking antibody that binds to TLR2 (aTLR2), both NF-κB phosphorylation and NF-κB nuclear translocation were significantly reduced. In addition, we evaluated the effect of *Hp*-OMVs on neurite function *in vitro*. The results show that conditioned media from astrocytes treated with *Hp*-OMVs reduced neurite number. Alternatively, the pre-treatment of astrocytes with aTLR2 prevented this effect. Taken together, *Hp*-OMVs may promote astrocyte reactivity and neural dysfunction through TLR2 engagement.

Disclosures: M.F. Gonzalez Castro: None. **A.F.G. Quest:** None. **L. Leyton:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.06/E19

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

Support: HK GRC grant 17101020
HK GRC grant 17100622
Hong Kong PhD Fellowship (HKPF)
HKU Presidential Scholarship (HKUPS)

Title: Evaluating of the profile of neuroimmune responses in the hippocampus induced by once or twice of bacterial endotoxin lipopolysaccharides

Authors: *K. OH[1,2], M. CHU[1,2], G. WONG[1], R. CHANG[2,3];
[1]Dept. of Anaesthesiology, Sch. of Clin. Medicine, LKS faculty of Med., [2]Lab. of Neurodegenerative Diseases, Sch. of Biomed. Sciences, LKS Fac. of Med., [3]State Key Lab. of Brain and Cognitive Sci., The Univ. of Hong Kong, Hong Kong, China

Abstract: Systemic inflammation can lead to neuroimmune responses with the polarization of macrophages/microglia. There has been increasing awareness of immune memory that can induce sustained immune responses in the body but such this phenomenon has not been investigated in the brain as microglia are the primary immune cells. To address this knowledge gap, we investigated the profile of neuroimmune responses after one (1x) or two (2x) injections of lipopolysaccharide (LPS, 0.5 mg/kg, i.p.) into 4-6 months old male C57BL/6J mice.The mice displayed significantly reduced locomotor activity (open field test) two weeks after of the LPS challenge. qRT-PCR showed the levels of mRNA expression for pro-inflammatory macrophages/microglia (IL-6, TNFα, CD86, Fgf2) were significantly increased in the hippocampus after LPS treatment in a dose dependent manner. However, the expression levels of IL-6 were higher in the hippocampus of 1x LPS mice than that of 2x LPS mice, and the levels of anti-inflammatory macrophages/microglia (STAT6, IL-10, ARG1, CD206) were significantly increased in the hippocampus after the 2nd injection of LPS. In addition, the levels of NADPH oxidase 1 (NOX1), IFN-γ, and stimulator of interferon genes (STING-1) were significantly increased in the hippocampus. Flow cytometric analysis revealed the number of CD11b+ (phagocytes), CD11b+CD45^low (microglia) as well as CD11b+CD45^high (macrophage-like cells) was significantly increased in the hippocampus after the LPS challenge. Furthermore, the number of mitochondrial DNA (mtDNA) was dramatically reduced in the CD11b+CD45^low (microglia) in the hippocampus of 1x/2x LPS mice. The number of mtDNA was reduced in the CD11b+CD45^high (macrophage-like cells) of 1x LPS mice, whereas it was increased after 2nd LPS injection. By using immunohistochemistry, the protein levels of ionized calcium binding adaptor molecule 1 and glial fibrillary acidic protein were relatively higher in the hippocampus of 1x LPS mice compared to that of 2x LPS mice. Furthermore, high level of cyclic GMP-AMP synthase (cGAS) was detected in the cytosol around the Golgi apparatus, and STING and p-STING expression were increased in the hippocampus after 2nd LPS injection.This study advances our understanding of whether immune memory in the brain is affected by non-sterilized systemic inflammation. Increased turnover of microglia occurs after the first wave of LPS treatment as it is evident by the loss of mtDNA. Second wave of microglial activation seems to be dependent on infiltrating macrophages triggered by the 2nd LPS. Consequently, microglia appear to have sustained activation even in the presence of anti-inflammatory factors.

Disclosures: K. Oh: None. **M. Chu:** None. **G. Wong:** None. **R. Chang:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.07/E20

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

Title: Dissecting the role of an antiviral immune response in a mouse model of Mitochondrial Disease

Authors: *M. GONZÁLEZ TORRES[1], P. BIANCHI[2], P. PRADA-DACASA[3], E. PUIGHERMANAL[2], M. LUNA-SÁNCHEZ[3], E. SANZ[3], A. QUINTANA[3];
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Abstract: Mitochondrial diseases (MD) are severe, untreatable, and often fatal disorders arising from mutations that affect the mitochondrial energy-producing machinery. MD exhibit a notable anatomical specificity, particularly affecting high-energy-demanding tissues, such as the brain. Among them, Leigh Syndrome (LS) is the most common pediatric MD. Mice lacking *Ndufs4* (Ndufs4KO) recapitulate human pathology, being a well-established LS animal model. Ndusf4KO mice undergo progressive neurodegeneration and neuroinflammation in specific brain regions, yet the mechanisms behind this susceptibility remain elusive. Recently, the immune response has gathered attention in MD research, as depleting microglia and macrophages ameliorates the pathology. Moreover, due to their bacterial origin, mitochondrial nucleic acids can be released into the cytoplasm in the context of mitochondrial dysfunction, triggering antiviral-like immune responses. In line with this, we have identified a robust upregulation of antiviral genes and proteins in affected brain areas of the Ndufs4KO mice. Our results show higher levels of type I interferon (IFN-I)-related proteins, as well as sensors of mitochondrial nucleic acids such as the double-stranded RNA sensor protein kinase R (PKR). To assess the contribution of the antiviral response to the pathology, we first focused on IFN-I-mediated responses by generating a Ndufs4KO mouse lacking IFN-I signaling (Ndufs4:Ifnar1dKO). While blocking *Ifnar1*-dependent signaling is not sufficient to ameliorate the clinical phenotype of the Ndufs4KO, it reduces the induction of antiviral and microglial markers. Subsequently, we explored the role of PKR by intravenous viral vector-mediated delivery of a shRNA targeting the expression of the PKR gene (*Eif2ak2*). Knocking down PKR expression significantly extended the lifespan of Ndufs4KO mice, highlighting the involvement of the antiviral response in disease progression. Furthermore, it reduced inflammatory markers, suggesting that PKR contributes to disease by exacerbating the neuroimmune response. Interestingly, we have identified PKR upregulation in microglia, a cell type critical for neurodegeneration in our animal model. Thus, to better understand the contribution of microglia to the disease, we performed RNAseq analysis of these cells, which confirmed that NDUFS4-deficient microglia upregulate antiviral and IFN-I genes, revealing a link between antiviral responses and microglia in MD pathogenesis. Overall, our findings provide novel insight into the role of an aberrant antiviral response in MD, paving the way for new effective treatments.

Disclosures: M. González Torres: None. **P. Bianchi:** None. **P. Prada-Dacasa:** None. **E. Puighermanal:** None. **M. Luna-Sánchez:** None. **E. Sanz:** None. **A. Quintana:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.08/E21

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

Support: NIEHS Grant #1R35ES035043-01

Title: Rotenone-induced mitochondrial damage activates the cGAS-STING pathway in astrocytes

Authors: *A. J. SCHULLER, O. A. YANOURI, S. M. ROCHA, R. B. TJALKENS; Envrn. and Radiologic Hlth. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Parkinson's disease (PD) is the fastest growing neurodegenerative disorder world-wide, yet remains etiologically idiopathic and incurable. While a majority of work seeking to mechanistically characterize the disease remains focused on dopamine neurons, mounting evidence supports a role of glial involvement in pathogenesis, even at time points preceding the neurodegenerative sequelae. Recently, the cGAS-STING nucleotide sensing pathway has been investigated as a potential therapeutic target in the context of MPTP and pre-formed fibril PD animal models. Still, our understanding of how this innate inflammatory pathway contributes to astrogliosis and the extent of this effect as neurotrophic or neurotoxic remains ill-resolved. Here, we sought to investigate the effect of acute rotenone exposure in mixed primary glial cells isolated from P1 C57BL/6 mouse pups to address this knowledge gap. We first established that the IC_{50} [Rotenone] = 78.90nM in this model via dose-response viability screening across 6- and 12-hour time points at half-log doses (1nM to 1000nM). We next explored the effects of modulating STING activation on cell viability using pharmacologic activator DMXAA and inhibitor H151. We report that 100µM DMXAA treatment reduces mixed glial viability to a similar extent as 30nM of rotenone (61.2% and 70.2%, respectively). 10µM H151 treatment was not sufficient to restore baseline viability, although it did slightly restore cell viability at 6 hours (77.1%). We further investigated the effect of rotenone exposure on the cGAS-STING pathway across 1-, 3-, and 6-hour timepoints using immunofluorescence microscopy and automated image analysis. p-STING Ser366 was significantly increased in rotenone-treated cells at all three time points and were rescued to baseline by treatment with H151. Pharmacologic inhibition of STING also resulted in significantly reduced cGAS levels across the three time-points. Further, rotenone significantly increased total cellular IRF3 area at 6 hours. These changes in cGAS-STING signaling were accompanied by increased release of IFN-ß in the supernatant of rotenone (2-fold) and DMXAA (3-fold) treated cells across at 1, 3, and 6 hours which was significantly reduced by H-151 treatment. Together with recent *in vivo* data from our group demonstrating the ability of short-term rotenone exposure to result in robust reductions in global DNA methylation and hydroxymethylation which precedes loss of dopaminergic neurons, these data warrant future exploration of the cGAS-STING pathway in the context of glial-mediated neuroinflammation and gene expression changes associated with PD.

Disclosures: A.J. Schuller: None. **O.A. Yanouri:** None. **S.M. Rocha:** None. **R.B. Tjalkens:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.09/E22

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

Title: Assessing the role of mitochondrial dsRNA as a trigger for neuroinflammation in a mouse model of Leigh syndrome

Authors: *M. GIRONA DEL POZO[1,2], M. GONZÁLEZ TORRES[3], P. PRADA-DACASA[3], P. BIANCHI[3], E. SANZ[4], A. QUINTANA[4];
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Abstract: Impairment of mitochondrial function has been associated to primary mitochondrial disease (MD), a group of severe and usually fatal pathologies. Among them, Leigh Syndrome (LS) is the most common pediatric MD, leading to neuronal affectation, motor and respiratory deficits, and premature death. Although the underlying mechanisms responsible for the neuronal death in these pathologies and LS remain mostly unknown, there is compelling evidence that the release into the cytosol of either mitochondrial DNA (mtDNA) or mitochondrial double-stranded RNA (mtdsRNA) induce pathogenic inflammatory responses. In this regard, results from our group using a mouse model of LS lacking the complex I subunit NDUFS4 (Ndufs4KO), indicate that the lack of the mitochondrial complex I subunit NDUFS4 in GABAergic neurons of the mouse olfactory bulb (OB) elicits a robust antiviral immune response and a noteworthy increase in the expression of cellular dsRNA sensors, as well as an increased presence of mtdsRNA associated to the dsRNA sensor protein kinase R (PKR). Moreover, we have found that silencing PKR expression decrease inflammatory markers in affected brain areas of Ndufs4KO mice, suggesting that PKR contributes to the disease progression by exacerbating the neuroimmune response. To elucidate the role of mtdsRNA signaling to the antiviral response in the Ndufs4KO mice, we have established a novel viral vector approach to achieve cell-type specific dsRNA degradation in GABAergic neurons, given that secreted brain RNAses play a key role in the degradation of both intracellular and extracellular RNA. To efficiently reduce mtdsRNA cytosolic actions, in a cell-type specific manner, we have generated a highly specific AAV vector for dsRNA expressing Spodoptera litura dsRNAse4 in a Cre-dependent manner, that was subsequently injected in the olfactory bulb of GAD2 neuron-specific conditional Ndufs4KO (Gad2-Cre;Ndufs4cKO) and control mice, as it is one of the most affected GABAergic brain regions in this mouse model.
Targeted degradation of mtdsRNA was first explored in vitro in HeLa cell cultures, and in the olfactory bulb of dsRNAse-injected Gad2-Cre;Ndufs4cKO mice compared to their respective control group. In addition, the neuroinflammatory status of this affected brain are was assessed after dsRNAse4 expression. Thus, our data suggests that targeted degradation of mtdsRNA may

prevent mitochondrial dysfunction-induced antiviral responses, presenting a potential avenue for the treatment of MD.

Disclosures: M. Girona del Pozo: None. **M. González Torres:** None. **P. Prada-Dacasa:** None. **P. Bianchi:** None. **E. Sanz:** None. **A. Quintana:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.10/E23

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

Support: R01NS112350
R01NS112308

Title: The chemokine, CCL2, is a potent pro-inflammatory inducer and establishes the baseline inflammatory profile of monocytes

Authors: *F. PAREDES[1], N. H. VARVEL[2], R. J. DINGLEDINE[3];
[1]Emory Univ., Decatur, GA; [2]Pharmacol., Emory Univ., Atlanta, GA; [3]Dept Pharmacol, Emory Univ. Sch. Med., Atlanta, GA

Abstract: Chemokine gradients are essential for hematopoietic-derived monocytic cells to extravasate circulation and enter inflamed tissues where they engage in the inflammatory response. Our previous work has shown that CCL2 is induced in the hippocampus within 30 minutes of seizure onset, culminating in the recruitment of CCR2+ monocytes into the brain. Genetic knockout of Ccr2, or CCR2 antagonism, blocked monocyte brain recruitment and alleviated the adverse pathological and behavioral effects of status epilepticus (SE). Here, we asked if CCL2/CCR2 signaling promotes a pro-inflammatory phenotype in monocytes. Recombinant CCL2 stimulated expression of the pro-inflammatory mediators, IL-1β, IL-6, TNF, HLA-DR, and CD80 and suppressed anti-inflammatory markers, IL-10, CD206, and CD163 in naïve THP-1 cells, a human monocytic cell line. Strikingly, the CCL2-induced inflammatory profile was nearly identical to that of lipopolysaccharide (LPS)-treated THP-1 cells, indicating that CCL2, on its own, is sufficient for pro-inflammatory polarization in THP-1 cells. Moreover, knockdown of endogenous CCL2 or CCR2 with siRNA or CCR2 antagonism abolished LPS-induced inflammatory polarization and, in the absence of LPS, elevated the expression of anti-inflammatory markers, IL-10, CD206, and CD163, similar to the effect of the potent anti-inflammatory cytokine, IL-4. CCL2 treatment promoted NFκB phosphorylation, which was blunted by CCR2 knockdown or AKT inhibition, linking the CCL2/CCR2/AKT pathway to NFκB activation. NFκB inhibition increased the basal expression of anti-inflammatory genes and reversed the pro-inflammatory effects of CCL2. These data together indicate that the activation of NFKB is essential for establishing the pro-inflammatory phenotype in response to CCL2 in monocytes. In line with our findings with THP-1 monocytes, splenocytes from CCR2 KO mice

exhibit elevated basal expression of anti-inflammatory markers compared to CCR2-sufficient mice. Systemic LPS administration increased the expression of pro-inflammatory markers in the spleen and hippocampus of CCR2-sufficient, but not CCR2 KO mice, further supporting a role for CCL2/CCR2 signaling in pro-inflammatory polarization in response to an inflammatory challenge. These results demonstrate that, in addition to its well-known chemokine role, CCL2 exerts powerful control over the inflammatory state of monocytes through the AKT/NFκB pathway and is essential to the monocytic response to LPS. This data provides insights into the regulatory mechanisms underlying monocyte phenotypic differentiation and offers a novel interpretation of the beneficial CCR2 modulation after SE.

Disclosures: F. Paredes: None. **N.H. Varvel:** None. **R.J. Dingledine:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.11/E24

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

Support: NIH R01AG061447
NIH R01AG061447

Title: Lithium inhibits inflammatory pyroptosis in human cortical NPC derived neurons and astrocytes

Authors: P. BHUIYAN[1], S. ANCHIPOLOVSKY[2], Y. YI[1], ***H. WEI**[3];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsylvnia, Philadelphia, PA; [3]Univ. of Pennsylvania, Cherry Hill, NJ

Abstract: Background: We postulated that lithium suppresses NMDA-driven upstream Ca^{2+} dysregulation via $InsP_3$ receptors ($InsP_3Rs$) overactivation and downstream mitochondrial dysfunction and oxidative stress that led to pyroptotic inflammatory pathways in human cortical NPC derived neurons and astrocytes. **Method:** Prior mixture of mature cortical neurons and astrocytes were differentiated from the ReNcell CX neuroprogenitor (NPC). Mixed cortical neurons and astrocytes were pretreated with lithium chloride (0.25, 1.5mM LiCl) for 3 days, then treated by N-methyl-D-aspartate (NMDA) at a toxic dose 50% (TD50, NMDA, 30μM) for 24 hrs. Cell viability were determined using both MTT reduction and LDH release assay. Mitochondrial oxygen consumption rate (OCR) was measured using Seahorse XF Cell Mito Stress Test assay. Immunoblotting measured type 1 $InsP_3R$ receptor expression, oxidative stress, and pyroptotic pathways activation associated proteins. ELISA analyzed inflammatory cytokines (IL-1β and IL-18). **Result:** Lithium inhibited NMDA induced-cell damage and death dose-dependently in mixed ReNcell cortical neurons and astrocytes. Lithium at clinically available low concentration (0.25 mM) inhibited the NMDA-mediated pathological elevation of basal OCR and proton leak (indicator of cell damage). Lithium inhibited NMDA-mediated increase of

$InsP_3R$-1 Ca^{2+} channel proteins. Lithium also inhibited NMDA-mediated pathological elevation of oxidative stress (4-HNE & MDA modified proteins) and suppressed pathological increase of pyroptosis activation proteins (NLR family pyrin domain containing 3 (NLRP3), caspase-1, N terminal gasdermin D (GSDMD-NT)). Lithium at 0.25 mM significantly inhibited inflammatory cytokine protein expression (IL-1β and IL-18). **Conclusion:** Lithium suppressed upstream Ca^{2+} dysregulation associated with the elevation of $InsP_3R$-1 and ameliorated downstream mitochondria dysfunction, oxidative stress and inflammatory pyroptosis, warranting further studies to repurpose lithium as a future effective drug for treating neuroinflammatory diseases.

Disclosures: P. Bhuiyan: None. **S. Anchipolovsky:** None. **Y. Yi:** None. **H. Wei:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.12/E25

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

Support: R01 NS116068 (JCG)

Title: The effects of liposomal clodronate on macrophage depletion following severe high-thoracic spinal cord injury

Authors: *S. KAUR[1], J. A. HUDSON[2], F. STAPENHORST FRANCA[1], R. KUMARI[1], A. BAUR[1], M. HASH[3], M. KYWERIGA[4], W. J. ALILAIN[5], S. P. PATEL[6], J. C. GENSEL[7]; [1]Univ. of Kentucky, Lexington, KY; [2]Univ. of Kentucky Spinal Cord & Brain Injury Res. Ctr., Lexington, KY; [3]SCoBIRC, Univ. of Kentucky, Lexington, KY; [4]Preclinical program, Novoron Biosci., San Diego, CA; [5]Dept. of Neuroscience/SCoBIRC, Univ. of Kentucky, Lexington, KY; [6]Spinal Cord & Brain Injury Res. Ctr., Dept. of Physiol., Univ. of Kentucky, Lexington, KY; [7]Physiology; Spinal Cord and Brain Injury Res. Ctr., Univ. of Kentucky, Lexington, KY

Abstract: The effects of liposomal clodronate on macrophage depletion following severehigh-thoracic spinal cord injury Sajeev Kaur, JayLa A. Hudson, Fernanda S. Franca, Reena Kumari, Anna Baur, Michael Hash, MichaelKyweriga, Warren J. Alilain, Samir P. Patel, and John C. Gensel[1]University of Kentucky, Department of Physiology, Spinal Cord & Brain Injury Research Center, Lexington,KY 40536-0509[2]University of Kentucky, Department of Neuroscience, Spinal Cord & Brain Injury Research Center,Lexington, KY 40536-0509[3]Department of Biomedical Engineering, College of Engineering, University of Kentucky, Lexington,KY 40536-0509[4]Novoron Biosciences, 1155 Island Avenue, Suite 100, San Diego, CA 92101**Abstract**Spinal cord injury (SCI) leads to an intraspinal inflammatory response including infiltrating bloodleucocytes. Some of these subsets of immune cells (monocytes) contribute to ongoing tissuedegeneration after SCI. Currently, there are no FDA-approved therapies for SCI. One promisingtherapy, clodronate liposomes (Formumax), depletes monocyte-derived intraspinal macrophagesand several independent laboratories have reported therapeutic

effects after lower thoracic SCI.The extent to which clodronate liposomes (CL) are effective after severe SCI or higher thoracic(T3) SCI is understudied. Here, we determined the effectiveness of CL after T3 SCI of multipleinjury severities. Adult female Wistar rats were subjected to T3 spinal contusion with two differentforces 300 kdyn (5s dwell time) and 400 kdyn (5s dwell time). For each severity, injured rats wererandomly divided into two groups, one group received 2 ml Clodronate (7mg/ml) on days 1, 3,and 6 post-injury (once a day) through tail vein injections, and the control group received vehicle(2 ml saline). Spinal cords were isolated 7 days post-injury and histological assessment will beperformed. Initial analyses reveal significant decreases in macrophage accumulation after T3injury. Ongoing studies will determine if macrophage accumulation and the magnitude of CL-mediated depletion are injury severity-specific. Identifying the effectiveness of CL across multipleseverities is clinically significant.

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Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.13/E26

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

Support: NIH Grant 2RF1 AG050518

Title: Neuroinflammatory measures following orexin/hypocretin expression manipulation in young and aged rats

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Abstract: The orexin/hypocretin neuropeptide system, primarily found in the lateral hypothalamus and perifornical region, modulates sleep, wakefulness, appetite, and cognitive function. One region with dense orexinergic projections is the basal forebrain, which is the major source of acetylcholine in the neocortex and limbic structures such as the hippocampus and amygdala. The basal forebrain cholinergic system mediates cognition and dysfunction is one of the key hallmarks of Alzheimer's disease. We have previously shown significant reductions in orexin expression and orexinergic innervation of cholinergic cells within the BF of aged rodents. Loss of orexin impairs cholinergic neurotransmission and cognitive function, but the mechanisms responsible for such deficits remain poorly understood. Recent evidence suggests neuroinflammation as a contributing factor to the pathogenesis of Alzheimer's disease. It has been suggested that orexin may be neuroprotective, and we hypothesize that the age-related loss

of orexin neurons diminishes the brain's anti-inflammatory response, leading to basal forebrain cholinergic dysfunction. Here, we administered lentivirus mediated expression of preproorexin antisense or sense into the lateral hypothalamus of young adult (3 months; antisense) and aged (22-26 months; sense), male and female Fisher 344/Brown Norway F1 hybrid rats. Three weeks later, a neuroinflammatory response was induced with an acute lipopolysaccharide (1 mg, intraperitoneal) challenge. Six hours later, brains were removed and bilaterally dissected with one hemisphere post-fixed in 4% paraformaldehyde for immunohistochemical analysis and one hemisphere frozen for cytokine analysis.Lentivirus efficacy was verified using immunohistochemistry for GFP expression and changes in orexin expression within the lateral hypothalamus and terminal regions. There was no significant difference in total Iba-1 in the basal forebrain, but there was a shift in activation state towards an activated, pro-inflammatory, "M1" phenotype in the orexin antisense treated rats. In addition, there was an increase in IL-6 and TNF-α in the prefrontal cortex of male rats with downregulation of orexin expression. Collectively, these data suggest that loss of orexin expression in aging may facilitate neuroinflammatory processes in key regions, such as the basal forebrain and prefrontal cortex, and thereby contribute to neurodegeneration and cognitive decline.

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Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.14/E27

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

Support: CIHR
Parkinson Canada

Title: Brain pericytes are highly sensitive to oxidative stress

Authors: *C. J. GROTEN[1], S. WENDT[2], L.-P. BERNIER[1], B. A. MACVICAR[3];
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Abstract: Brain dysfunction in various disorders such as stroke, Parkinson's, and Alzheimer's disease is promoted by oxidative stress, a pathological state resulting from an excess of reactive oxygen and nitrogen species. These molecules impede brain function by oxidizing various proteins and lipids which impact essential cellular processes and can ultimately lead to neuronal dysfunction and death. Hence, it is crucial to identify the primary cellular and molecular targets that are impacted by oxidative stress and contribute to brain dysfunction. To address this, we

assessed cell death evoked by oxidative stress in acute cortical brain slices from rodents by measuring propidium iodide (PI) uptake with two-photon microscopy. Oxidation of thiols on proteins and glutathione is a prominent downstream impact of reactive oxygen and nitrogen species. Therefore, we triggered oxidative stress in acute brain slices using thiol oxidation. We observed that exposure of brain tissue to a thiol oxidizing agent was sufficient to induce cell PI loading, indicating cell death. Interestingly, this cell death largely occurred in cells associated with the vasculature rather than non-vascular cells. Moreover, the uptake of PI by these vessel-associated cells occurred rapidly, within 10 minutes after thiol oxidation. Given their distinct morphology and association with blood vessels, we explored the possibility that these vulnerable cells were pericytes. Utilizing live imaging of pericytes labeled with the fluorescent marker NeuroTrace (NT), we discovered that oxidative stress led to concurrent PI uptake and NT loss in a significant portion of pericytes-indicating robust cell death. Our findings demonstrate that pericytes possess high sensitivity to thiol oxidation, which is a consequence of reactive oxygen species production and oxidative stress. Pericytes are implicated in the regulation of blood vessel stability, the integrity of the blood-brain barrier, and cerebral blood flow. Consequently, our data suggests that dysfunction of pericytes might significantly contribute to brain pathologies triggered by oxidative stress. Future investigations aimed at unraveling the mechanisms underlying the heightened susceptibility of these cells to cell death during oxidative stress will be essential to test this hypothesis.

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Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.15/E28

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

Support: NS114891
NS122918

Title: Do neutrophils aid the in-vivo conditioning lesion response?

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Abstract: The in vivo conditioning lesion response is a well-known process that enhances the regeneration in the peripheral and central nervous systems. An initial or conditioning lesion will accelerate axonal regeneration after a second injury. In the peripheral nervous system, macrophages are suggested to promote regeneration. However, in the last decade, neutrophils' role in neurological diseases and injuries has expanded as they have been shown to have both positive and negative effects. Neutrophils have been shown to have pro-regenerative effects on axonal regeneration in the central nervous system. To examine the role of neutrophils, we used a

Cxcr2 knockout (KO) mouse, which we have shown to decrease neutrophil homing while not affecting macrophage accumulation. Wild type and *Cxcr2* KO conditioning injury was a right-side sciatic nerve transection, while the left side was an operative control. Seven days later, the right-side nerve was crushed 4 mm proximal to the transection injury, and the left was crushed as well. Two days later, the nerves were harvested and fixed. The nerves were then sectioned (40 μm) and stained for SCG10 to label regenerating sensory axons. Z-stack images of each specimen were collected, and then axon length was calculated using Image J. No difference was detected between the wild type and Cxcr2 KO mice. In a separate experiment, we used a Ly6G antibody neutrophil depletion strategy to reduce neutrophils. We used *Ccr2*-GFP knock-in/knockout mice, which are known to have a decrease in the number of infiltrating macrophages. Ly6G or control antibody treatment (intraperitoneal injection) was started the day before the conditioning lesion. Animals received treatment daily. No difference was detected between Ly6G and control antibody treatment. These results suggest that neutrophils are not required for the conditioning lesion response. To further investigate the role of macrophages and neutrophils in the in vivo conditioning lesion response, we will utilize a CD11b-thymidine kinase mouse. This mouse line has previously been shown to deplete both macrophages and neutrophils significantly. Using this model, we will determine if the conditioning lesion response is affected when both macrophages and neutrophils are depleted.

Disclosures: B.M. Balog: None. **R.E. Zigmond:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.16/E29

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

Support: Undergraduate Mini Grant
Lafayette Parish Endowed Professorship
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McNair Scholars Program
NIMH

Title: High fat diet and Fgfr1 inactivation effects on neuroinflamation phenotypes in the hypothalamus and hippocampus

Authors: *J. STAGRAY[1], A. CHISTOSERDOV[2], J. RICHARD[2], C. HEALEY[2], T. PRATHER[3], J. FISER[2], S. ASHMORE[2], G. MEAUX[2], A. FAUL[2], G. NORA[2], J. MALAHMEH[2], K. M. SMITH[2];
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Abstract: FGFR1 is an important receptor involved in mediating neuroendocrine based signaling across blood brain barriers. FGFR1 is highly expressed within the hypothalamus and hippocampus. FGF21 is one of these neuroendocrine hormones that is produced by liver cells to modulate feeding behaviors through the activation of MAPK signal transduction pathways. Within the 3V, there is a specialized radial glia-like cell known as tanycytes. Tanycytes are found along the medial and ventral walls of the third ventricle (3V). α and β tanycyte cell bodies interact with CSF. The α tanycyte projections extend into adjacent hypothalamic nuclei which are responsible for governing feeding behavior circuitry. Meanwhile, β tanycyte projections interact directly with fenestrated capillaries of the medial eminence to assist in the transportation of metabolites and neuroendocrine cues. They are also poised to respond to FGF21 and other circulating FGF ligands. Tanycytes have an ability to participate in glucose homeostasis mechanisms through GLUT expression. When exposed to a high fat diet that has been shown to induce diabetes, tanycytes undergo a transition from radial glia-like phenotypes into a more reactive astrocyte phenotype. Within an Fgfr1 inactivated mouse model system, we have previously shown that this diet results in a more elevated blood glucose concentration within both male and female cKO groupings compared to control littermates; however, we have observed a more severe elevation in the female cKO grouping. Here we measure GFAP, Vimentin, SOX2, and IBA-1 cellular markers to assess the severity of phenotypes relating to astrocytes, glial stem cells, and microglia along the 3V and DG.

Disclosures: J. Stagray: None. **A. Chistoserdov:** None. **J. Richard:** None. **C. Healey:** None. **T. Prather:** None. **J. Fiser:** None. **S. Ashmore:** None. **G. Meaux:** None. **A. Faul:** None. **G. Nora:** None. **J. Malahmeh:** None. **K.M. Smith:** None.

Poster

PSTR456: Neuroinflammation: Beyond Microglia

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR456.17/E30

Topic: F.03. Stress and the Brain

Title: IL-17A as a regulatory factor to regulate obesity-induced neuroinflammation in the brain

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Abstract: Obesity is associated with metabolic syndrome and chronic inflammation, affecting various physiological systems such as the central nervous system (CNS) and the immune system. Interleukin-17A (IL-17A), predominantly produced by T helper 17 (Th17) cells, are pivotal in the development of neurodegenerative diseases, including mood disorders. Although Th17 cells have been identified as regulators of the severity of metabolic diseases linked to obesity, the role of IL-17A in mood disorders associated with obesity has not been investigated. In our present study, we provided evidence showing increased plasma IL-17A levels and striatal IL-17A gene expression following chronic feeding by high fat diet (HFD) for 3 months. We then conducted

the in vivo study by administering IL-17A intraperitoneally into mice once every two days for a month. Behavioral assays using the open field test and elevated plus maze analysis revealed that peripheral IL-17A administration induced anxiety-like and depressive-like behaviors in mice. Additionally, microgliosis was observed in multiple brain regions of IL-17A-treated mice, including the anterior cingulate cortex (ACC), caudate putamen (CPu), corpus callosum (CC), and hypothalamus. Furthermore, there was a significant increase in reactive astrocytes with S100β immunoreactivity in the ACC, CPu, and CC. These brain regions correspond to areas exhibiting neuroinflammation in our previous study under conditions of long-term HFD feeding. The findings suggest that the upregulation of peripheral IL-17A in obesity contributes to neuroinflammation in specific brain regions, potentially leading to the development of mood disorders. This study also sheds light on the underlying molecular mechanisms linking metabolic syndrome-associated immune responses and mood disorders.

Disclosures: J. Fu: None. **S. Tzeng:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.01/E31

Topic: C.09. Stroke

Support: NIH R56 NS126748
KAKENHI 21K17789

Title: Self-organizing recruitment of compensatory areas maximizes residual motor performance of upper extremity post-stroke

Authors: *V. BARRADAS PATINO[1], K. LEE[2], N. SCHWEIGHOFER[2];
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Abstract: Although previous clinical and experimental work shows orderly recruitment of compensatory motor cortical areas as a function of the size of cortical lesions affecting upper extremity functions, the underlying mechanisms are unknown. Here, we hypothesize that the recruitment of compensatory motor areas follows optimal control principles to maximize motor performance while minimizing effort by means of a plastic process based on reinforcement learning limited by anatomical constraints imposed by the lesion. In addition, a homeostatic regulation process concurrently maximizes information transfer in the lesioned neural networks to create appropriate baseline conditions for the reinforcement learning process to be effective. To test this hypothesis, we built an adaptive neuro-musculoskeletal model consisting of a simplified planar arm controlled by ipsi- and contralesional primary motor cortices, a pre-motor cortex, and a spinal motor neuron pool. To learn control of the arm, the excitability of spinal motor neurons is modified via homeostatic regulation, and synapses in the cortical areas are updated via reinforcement learning. The intact model reproduced neurotypical individuals'

neural, muscular, and behavioral results. As the lesion size increased, the model exhibited progressive recruitment of the remaining primary motor cortex, the premotor cortex, and the contralesional cortex. In addition, as seen in actual brains, the compensatory activity in the premotor and contralesional motor cortex was larger in the early recovery period than in the late recovery period. Analysis of the plasticity in individual areas showed that: 1) The premotor cortex acts as a reserve area that enables the recovery of fine motor control, analogous to the motor cortex. 2) The contralesional cortex acts as a reserve area that avoids paralysis at the price of poor independent joint control. 3) Spinal motor neuron plasticity enables force generation following a large lesion that weakens the input from the corticospinal region. Our results suggest that biologically plausible plastic processes, which are ongoing whether the brain is intact or lesioned, can lead to the self-organizing recruitment of compensatory areas that maximize residual motor performance following strokes of different sizes.

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Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.02/E32

Topic: C.09. Stroke

Support: AHA Grant 20PRE35210339

Title: The quantification of stretch reflex excitability during volitional reaching in chronic hemiparetic stroke

Authors: *T. A. M. PLAISIER[1], J. A. BEAUCHAMP[2], A. ACOSTA[1], J. P. A. DEWALD[1]; [1]Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Stretch reflex modulation during the execution of movements is achieved by supraspinal structures via corticofugal pathways. This allows for high movement accuracy even in unpredictable environments. Quantification of reflex excitability during voluntary movement can be used as a proxy measure of neural activity and descending drive from supraspinal structures. This allows further study and understanding of how these structures affect movement, and how supraspinal neural injuries following a stroke may affect stretch reflex modulation and upper limb function.
We have developed a novel protocol and robotic platform to quantify stretch reflex excitability during a ballistic reaching task. The robotic platform is a newly developed haptic device called NACT-3D which allows users to make multijoint movements with minimal added effort in the horizontal plane, combined with 20 cm of vertical movement to allow for shoulder abduction/adduction movement and loading. The device is capable of applying ramp stretch perturbations to the forearm resulting in elbow rotation perturbations at 360 °/s over 50 ms time

periods. Participants were asked to move as fast as possible between a near and a far target at different distances in front of their sternum, with perturbations occurring in random catch trials prior to movement, at movement onset, and at 50% of peak movement velocity. Reflexive muscle activity in the biceps and triceps brachii was measured during short (25-75 ms) and long (75-125 ms) latency reflex time windows following the perturbation.
Pilot experiments have been performed on a group of participants with chronic hemiparetic stroke (n = 6) and control participants (n = 2). Preliminary results show that the robotic platform was able to elicit stretch reflexes before and during movement in the paretic limb of moderately to severely impaired stroke participants. Reflexive muscle activity during movement was altered in hemiparetic stroke, with an increase in biceps and a decrease in triceps activity during the short-latency reflex time window. The brief, high-velocity perturbations allow for studying both muscle activity and joint torque following the perturbation. Further data collection and group-level analysis is underway.
The initial results indicate a disruption in stretch reflex modulation, and for the first time show altered stretch reflex modulation during movement following hemiparetic stroke. The developed protocol and device allow for studying stretch reflex modulation during a variety of motion tasks and will increase our understanding of the complex role of supraspinal structures in stretch reflex modulation post hemiparetic stroke.

Disclosures: T.A.M. Plaisier: None. **J.A. Beauchamp:** None. **A. Acosta:** None. **J.P.A. Dewald:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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Topic: C.09. Stroke

Support: This research was supported by the California Institute of Regenerative Medicine (TRAN1-12891 & DISC2-15137).

Title: Leveraging molecular and motion-based behavioral approaches to profile post-stroke responses

Authors: *Á. CRUZ-LOCIEL, A. PANDITRAO, K. GEFEN VLASSOPOULOS, E. GONZALEZ CUBERO, I. L. LLORENTE;
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Abstract: Ischemic stroke is a devastating disease that affects >795,000 patients per year in the United States and accounts for ~87% of all stroke types. Infarcts are caused by a blockage of the blood supply to the brain when a thrombotic or embolic clot blocks a vessel. This can occur in large blood vessels, such as those affected by cortical stroke (CS), or in deep penetrating vessels, such as those affected by subcortical white matter stroke (WMS). While infarction in the cortex

typically produces an acute injury, white matter infarcts can progress over time and develop into vascular dementia. Despite current treatment modalities, there exists a lack of disease-modifying therapeutics in the clinic partly because there are still gaps in knowledge regarding the specific responses across brain regions after injury. To address this issue, single-cell and spatial RNA sequencing technologies have provided the capacity to understand cell and anatomic transcriptional signatures in disease models. Considering this, single-nuclei RNA sequencing and spatial transcriptomics will be utilized to characterize tissue-specific changes during the subacute and chronic phases of ischemia in young male mice subjected to CS and WMS. These results will be accompanied by histological analyses of cellular and axonal markers as well as motion-based behavioral readouts through Motion Sequencing (MoSeq) analysis. Preliminarily, MoSeq analysis detected significant ($p<0.05$) behavioral motif signatures between stroked and age-matched controls. These observations suggest that static motifs comprise most of the behaviors from stroked mice compared to healthy controls. Overall, these techniques should provide insight into cell-specific and behavioral profiles of brain ischemia and help us generate precise hypotheses about the underlying pathophysiology before proceeding to therapeutic interventions. Future experiments will include aged male and female mice in our workflow.

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Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.04/E34

Topic: C.09. Stroke

Support: 5T32HD101395-02
1R01NS105759-01A1

Title: Quantifying the Effect of Trunk Postural Control on Reaching Deficits Post Hemiparetic Stroke

Authors: *K. C. SUVADA[1], J. DEOL[2], J. P. DEWALD[1], A. ACOSTA[1];
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Abstract: The trunk provides a stable base of support to the upper body and facilitates proper interaction with the environment. Damage to descending corticospinal pathways after a stroke alters performance of activities of daily living and in particular, reaching. Despite the highly coupled nature of the trunk and arm, the impact of a stroke on coordinated trunk and arm reaching remains largely unknown. This is especially true in the context of the flexion synergy (involuntary flexion of the elbow, wrist, and fingers during shoulder abduction). The goal of this study was to quantify reaching ability post stroke with the trunk unrestrained. We hypothesize

that deficits present due to the flexion synergy will be exacerbated when actively controlling the trunk.9 individuals with hemiparetic stroke (64.11 ± 6.57 years old; Fugl-Meyer Assessment (FMA) 7-42/66; Reaching Performance Scale (RPS) 0-13/36; and Trunk Impairment Scale (TIS) 12-16/23); and 4 age-matched controls (66.25 ± 0.96 years old) participated in the study. The trunk and arm were instrumented with motion capture markers to quantify arm kinematics offline. Individuals sat in a Biodex chair with the trunk either restrained or unrestrained. Participants were asked to reach while their arm was fixed to a robotic device capable of generating a frictionless table environment and imposing downward forces equal to 25% or 50% of their maximum shoulder abduction force. Reaching distance (RD) was computed in a coordinate system in the plane of the arm with the origin at the estimated location of the glenohumeral joint (Meskers, 1998) and normalized to limb length. A generalized linear mixed effects model was used to assess the effect of load and restraint on RD in stroke and control participants. The relationship between RD and the clinical measures was evaluated using linear regression.Consistent with past studies, limb loading resulted in reduced RD for the paretic limb ($p<.05$) but not in the non-paretic limb nor in the dominant limb of controls. For all three participant groups, there was an effect of trunk restraint on RD, with reduced RD when the trunk was unrestrained ($p<.05$). RD was positively correlated with FMA (unrestrained: $p=0.02$ and restrained: $p=0.05$) and RPS (only restrained: $p = 0.03$). While there was an effect of trunk restraint on reaching distance, flexion synergy was the major impairment impacting reaching ability with reduced RD at increasing shoulder abduction loading. Future work will further examine the underlying motor control of reaching with and without trunk restraint based on trunk and arm muscle electromyography.

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Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

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Topic: C.09. Stroke

Support: NIH Grant

Title: Determine whether norepinephrine amplifies the commands of indirect motor pathways

Authors: *M. SEREIKA[1], J. YAO[2], J. P. DEWALD[2];
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Abstract: Background: Following a stroke impacting upper limb function, there is an increased usage of pathways from the contralesional hemisphere when activating shoulder abductor muscles in the paretic upper limb. This is linked to the expression of coactivation of shoulder abductors and elbow/wrist and finger flexors, or the flexion synergy. The indirect

corticobulbospinal motor pathways from the contralesional hemisphere are typically weaker than corticospinal pathways. Since there is evidence suggesting increased motor neuron excitability from a greater spinal presence of NE post hemiparetic stroke this may facilitate the use of these indirect motor pathways as well as explain the presence of hyperactive stretch reflexes or spasticity. Work by McPherson et al., found that the administration of TIZ, a NE agonist with *a*2 affinity, resulted in a significant decrease in flexion synergy. They suggest TIZ decreased NE, resulting in reduced hyperexcitability of the motor unit and made it less efficient for corticobulbospinal pathways to control the paretic limb. This preliminary work aims to investigate how reducing motor neuron hyperexcitability using TIZ affects the utilization of lesional and contralesional motor cortices and pathways for upper limb control. This experiment was conducted both before and after the administration of a single dose of TIZ or placebo. Using electroencephalography (EEG) and electromyography (EMG) signals, we quantified the connectivity of both the lesioned and contralesional hemispheres to muscles of the paretic upper limb using corticomuscular wavelet coherence. **Hypothesis and Preliminary Results:** We hypothesize that TIZ-induced decrease in NE levels will result in a decreased corticomuscular coherence between the contralesional hemisphere and the paretic upper limb. Simultaneously, spared pathways from the lesioned hemisphere may be recruited to complete a motor task, reflected by an increased corticomuscular coherence between the lesioned hemisphere and the paretic arm. Our preliminary findings are showing an increase in corticomuscular coherence between the lesioned hemisphere and the paretic deltoid post-TIZ administration. Additionally, laterality index measurements found TIZ resulted in a decreased use of the contralesional hemisphere during shoulder abduction.**Conclusions:** Our goal is to better understand how motor cortical and motor pathway recruitment changes after decreasing NE in stroke. We hope to uncover the presence and the effect of neuromodulatory changes post-stroke as this will inform future research directions and the design of more effective targeted rehabilitation interventions.

Disclosures: M. Sereika: None. **J. Yao:** None. **J.P. Dewald:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

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Topic: C.09. Stroke

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Title: Interrogation of cerebral cortex reorganization after stroke using transcranial focused ultrasound stimulation

Authors: *S. SUN[1], C.-F. V. LATCHOUMANE[1], E. PIRONDINI[2], R. WANG[3], Q. BARRAUD[4], K. GALAN[3], F. C. HUMMEL[4], J. BLOCH[1], G. COURTINE[4];
[1]CHUV, Lausanne, Switzerland; [2]Rehabil. and Neural Engin. Labs., Univ. of Pittsburgh, Pittsburgh, PA; [3]EPFL, Lausanne, Switzerland; [4]EPFL, Geneve, Switzerland

Abstract: Recovery from stroke involves phase-dependent reorganization of the cerebral cortex. However, the contribution of each reorganizing region in the control of movement remains unclear. One of the limitations to address this question is lack of causal interrogation tools that allows longitudinal investigation of the functional contribution of spatially-defined regions of the brain. Transcranial focused ultrasound (tFUS) is a novel non-invasive neuromodulation technology with high spatial resolution, deep penetration and reversibility. We propose that tFUS can be leveraged to evaluate the contribution of different regions of the cerebral cortex during the natural recovery of movement following a stroke. However, understanding and selection of tFUS parameters remains a challenge. Moreover, most of the existing studies have been unsuccessful in identifying tFUS protocols with significant neural or behavioral impacts. In this study, we conducted a systematic validation method to identify tFUS parameters inducing a transient “loss of function” during the performance of well-controlled upper limb movements. We designed a movement triggered tFUS system that delivered stimulation while non-human primates (NHP) were performing a reach-and-pull task. With this online stimulation setup, we mapped a large number of tFUS parameters sets, and converged to parameters that maximized the disruption of the behavior. We then evaluated the obtained parameter set in “online” and “offline” conditions when the NHPs were performing a more difficult behavioral task and verified the reduction of cortical excitability with electrophysiological assessments. We then applied our validated tFUS protocol to interrogate the contribution of the primary motor cortex (M1) from the ipsilesional and contralesional hemispheres to the production of upper-limb movements during recovery from after a stroke located in the internal capsule. Our results show that tFUS applied over the contralesional M1 caused an increased pulling duration post-stroke, but not pre-stroke. This result was consistent with various prior studies that emphasized the important role of the contralesional M1 in supporting upper limb functional recovery post-stroke. Finally, we validated the protocols developed in NHP models for application in humans, showing that the application of tFUS over the hand region of M1 induced a reversible, yet sustained decrease in the amplitude of TMS-induced motor evoked potentials in hand muscles of healthy participants. This study provides a guideline to interrogate the functional role of spatially-defined regions of the brain on the production of movement using tFUS.

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Poster

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Topic: C.09. Stroke

Support: Heart and Stroke Foundation of Canada
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Title: Level of impairment affects brain metabolic activity during complex walking tasks in persons with chronic subcortical stroke

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Abstract: The balance of neural activity between hemispheres becomes altered post-stroke, and this imbalance may impede gait recovery. Non-invasive brain stimulation can be utilized to lessen interhemispheric imbalances. However, results of stimulation to recover gait post-stroke have been inconstant, potentially due to improper protocols linked to poor understanding of specific individuals' pathophysiology. This study examined relationships between brain metabolic activity, asymmetries, and impairment level in persons with stroke. Changes in cerebral glucose metabolism were measured with ^{18}F-fluorodeoxyglucose positron emission tomography in 5 individuals with a chronic subcortical stroke (age range: 56-73, mean time since stroke: 35 months) and 7 healthy controls (age range: 55-63) during a complex walking task relative to a simple walking task. In the complex task, participants navigated around cones placed in an unpredictable order, creating an irregular walking trajectory. In the simple task, participants walked straight between cone-delineated lanes. Impairment level was determined by the Chedoke-McMaster Stroke Assessment (CMSA) scale and National Institutes of Health Stroke Scale (NIHSS). Complex walking was compared to straight walking using a whole-brain voxel-wise analysis in a flexible factorial design in SPM12. Asymmetry was examined using a laterality index based on the number of suprathreshold voxels in each hemisphere on a Z-map at a threshold of $p<.01$. During the complex task, controls showed no significant difference in interhemispheric activity ($p>.05$) and increased activity during complex walking, especially in the superior parietal lobule (SPL; 4.3±2.4%). Those with stroke had a decreased signal bilaterally in the SPL (contralateral: -2.9±2.9%, ipsilateral: -2.4±1.3%, $p=.002$). Participants with stroke displayed more asymmetry in the SPL and primary motor cortex, but less in the prefrontal cortex in the complex task. SPL asymmetry correlated with CMSA ($r_s=0.97$, $p<.005$) and NIHSS ($r_s=-0.97$, $p<.005$) scores, where more impaired subjects activated the contralesional SPL and less impaired subjects activated the ipsilesional SPL. Metabolic activity asymmetry during complex walking depends on stroke impairment level, extending prior models of interhemispheric asymmetry as a function of stroke severity to gait. These findings highlight the SPL as a potential brain stimulation target for gait recovery. Since interhemispheric activity differs with impairment level, impairment level must be considered when developing individualized stimulation protocols for post-stroke gait rehabilitation.

Disclosures: S. Perfetto: None. **T. Mitchell:** None. **F. Starrs:** None. **J. Minuk:** None. **J. Soucy:** None. **A. Thiel:** None. **C. Paquette:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.08/E38

Topic: C.09. Stroke

Support: R01HD091492-04

Title: Decreased contralesional cortical excitability in individuals with moderate to severe upper limb hemiparesis: A secondary analysis

Authors: E. KING[1], F. J. DAVID[2], M. P. TREVARROW[2], S. URDAY[3], L. C. GOELZ[5], B. CLELAND[6], S. MADHAVAN[7], ***M. STOYKOV**[8,4];
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Abstract: Background and Purpose: The role of the contralesional hemisphere in post-stroke recovery is not clearly defined. Some post-stroke recovery models suggest that the role of the contralesional cortex may be related to the amount of ipsilesional reserve. However, this relationship remains to be elucidated. In the current study, we investigated the relationship of contralesional excitability to upper limb impairment, ipsilesional excitability, and various demographics in individuals with chronic moderate to severe upper limb impairment post-stroke. Of note, this is a secondary analysis of baseline data obtained from a clinical trial (NCT03517657). **Methods:** In 30 participants, we used stepwise linear regression to examine the relationship between contralesional resting motor threshold (RMT), our dependent outcome, which was used as a measure of cortical excitability, and the following independent outcomes: 1) Fugl-Meyer Assessment for the Upper Extremity scores; 2) Motor Evoked Potential status (MEP + or -) of the ipsilesional hemisphere; 3) normalized ipsilateral silent period (iSP) depth from ipsilesional to contralesional hemisphere, 4) contralesional MEP latency; 5) age; and 6) years since stroke onset. **Results:** The most parsimonious statistical model to predict contralesional RMT included the intercept and MEP status ($F1, 28 = 15.97$, $p = 0.0004$, adjusted R-square = 0.34). The RMT of the MEP+ group was significantly lower than the MEP- group (estimated mean difference ± SE = 19.7 ± 4.9; t-value = 4; $p = 0.0004$). **Conclusions:** Our preliminary data indicates that contralesional excitability was reduced in participants who were MEP- in the ipsilesional hemisphere relative to MEP+ participants. This unique finding suggests an overall down-regulated system in MEP- individuals and important knowledge for the field of stroke recovery. We will be presenting baseline data of all participants (N=75) who have completed this experimenter-blinded randomized controlled trial.

Disclosures: E. King: None. **F.J. David:** None. **M.P. Trevarrow:** None. **S. Urday:** None. **L.C. Goelz:** None. **B. Cleland:** None. **S. Madhavan:** None. **M. Stoykov:** None.

Poster

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Topic: C.09. Stroke

Support: NIH Grant R01NS058667
NIH Grant R03HD094615
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NIH Grant T32EB025766
NIH Grant TL1TR001423

Title: New insights into atypical corticospinal tract microstructure in children with hemiparetic cerebral palsy

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Abstract: Unilateral brain injuries in early childhood can result in hemiplegic cerebral palsy (HCP), characterized by deficits such as hand weakness[1,2] and loss of independent motor control between hands, known as mirroring.[3,4] The objective of this diffusion MRI (dMRI) study is to investigate the relationships between atypical corticospinal tract (CST) development and quantitative measures of hand impairments. Structural scans were acquired and used to identify anatomical regions of interest using a standardized atlas.[5-7] Five cortical areas with typical or potential CST connectivity were masked with the CST to determine the overlap volume, then normalized by the total volume of the CST. dMRI data were acquired and pre-processed as previously described.[8,9] Anatomical landmarks were used to guide probabilistic tractography of the CST to calculate the mean and standard deviation of diffusivity metrics (FA, MD, AD, RD). Grip strength and mirroring were measured using simultaneous recording of two handheld digital dynamometers.[10] Spearman correlation analyses were performed with age and sex as covariates. A Mann-Whitney U test was performed between participants with HCP and controls. Statistical significance was set at $p<0.05$. Results include 15 children with early-onset HCP (7M, 13.8±6.0y) and 13 controls (5M, 14.4±6.3y). For participants with early-onset HCP, there was a significant positive correlation between MD in the ipsilesional CST and grasp weakness severity (rho=0.63, p=0.021) and a significant positive correlation between RD in the ipsilesional CST and grasp weakness severity (rho=0.68, p=0.011). There was also a significant negative correlation between FA in the contralesional CST and hand mirroring severity (rho=-0.67, p= 0.013) that was primarily driven by a positive trend between RD in the contralesional CST and hand mirroring severity (rho=0.49, p=0.088). In the non-lesioned hemisphere, there was a

significant decreased density of tract termination in the precentral gyrus for HCP participants in comparison to controls (p=0.044). Conversely, there was an increased density of tract termination in the non-lesioned superior parietal gyrus for HCP participants in comparison to controls (p=0.039). Here, we show that in individuals with early-onset HCP there is a significant relationship between supraspinal neural microstructure and impairments in normal hand function. HCP presents with unilateral motor deficits; however, these results show an injury early in development can have detrimental effects on the non-lesioned hemisphere, specifically the motor pathways and association areas, and involvement of the unaffected hand.

Disclosures: A. Hruby: None. **D. Joshi:** None. **J.P. Dewald:** None. **C. Ingo:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

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Program #/Poster #: PSTR457.10/E39

Topic: C.09. Stroke

Support: NIH Grant 5T32EB009406-13
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Title: Heterogeneity in the Expression of Weakness and Flexion Synergy during Early Recovery after Stroke

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Abstract: The first 90 days following a stroke have been identified as a critical time-period for motor recovery. The presentation of upper limb motor weakness and flexion synergy (e.g., involuntary coupling of proximal shoulder abduction and distal elbow flexion) occur during this period. Latest scientific evidence suggests that hyperexcitable spinal motor neuron pool due to an increased presence of monoamenergic neurotrasmitters amplifies the descending ionotropic drive from the less-potent indirect pathways (e.g., reticulospinal tract), which underlies the expression of flexion synergy. While weakness may improve in general as the drive through the corticospinal tract recovers, flexion synergy expression may diverge based on the excitability of the spinal motor neuron pool. This preliminary work, using data collected from an ongoing study, aims to investigate differences in expression between weakness and flexion synergy. We hypothesize that as individuals overcome weakness and begin to recover motor function, flexion synergy expression may not progress in a similar manner due to the distinct underlying mechanisms. Data were collected from participants with severe to moderate impairments in an inpatient rehabilitation facility over multiple sessions. In each session EMG and torque were measured while the participant generated isometric maximum voluntary torque (shoulder

abduction), with the paretic arm. EMG signals were processed and normalized to the maximum value across all measurements. Flexion synergy was quantified as the normalized biceps EMG 50ms prior to the peak shoulder abduction torque. Participants initially began with various levels of strength (2.52-19.3 Nm). Flexion synergy expression also was variable across participants (10.9-80.5 % Bicep Activation). There were distinct patterns seen within the participant group with individuals with weakness also having weak flexion synergy expression, strong individuals with strong flexion synergy expression, and weak individuals with strong flexion synergy expression. There was heterogeneity between the expression of weakness and flexion synergy. This could be because strength measurements involve activation from both lesioned and non-lesioned hemispheres, as a sum of output from the entire nervous system while flexion synergy closely measures the spontaneous activation coming from ipsilesional reticulospinal drive. The next step towards understanding the mechanisms behind flexion synergy would be to incorporate established methods for precisely measuring motor neuron excitability. Our goal is to better understand how the nervous system controls motor function after stroke.

Disclosures: A. Smith: None. **H. Sohn:** None. **M.D. Ellis:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

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Program #/Poster #: PSTR457.11/E40

Topic: C.09. Stroke

Support: NIH R01 HD109157
NSF 2401215

Title: The Expression of Flexion Synergy Enhances Spasticity in Stroke

Authors: *J. SUNG[1], M. RAJABTABAR[1], B. MULYANA[1], H.-T. PENG[1,2], Y. YANG[1,2,3]; [1]Bioengineering, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Clin. Imaging Res. Center, Stephenson Family Clin. Res. Institute, Carle Fndn. Hosp., Urbana, IL; [3]Dept. of Physical Therapy and Human Movement Sciences, Northwestern Univ., Chicago, IL

Abstract: Following a stroke, the contralateral arm on the opposite side of the damaged hemisphere exhibits abnormal co-activation of shoulder abductor and elbow flexor muscles, clinically known as the flexion synergy. Previous study suggested that the expression of flexion synergy may influence the already overactive stretch reflexes in affected elbow flexors. Therefore, this study aims to quantitatively analyze the impact of flexion synergy expression on elbow flexor stretch reflexes in stroke, in comparison to muscle pre-activation induced stretch reflexes in controls.
The early phase data collected in this study include two chronic stroke participants and three age-matched able-bodied control individuals. Stroke participants were precisely controlled for three levels of flexion synergy induced by shoulder abduction effort (0%, 20%, and 40% MVC) of the

paretic arm. Simultaneously, a robotic device was utilized to induce stretch reflexes by extending the elbow at a sufficiently fast speed (peak value 270°/s) to evoke stretch reflex (50-150 ms). In the control group, voluntary elbow flexor pre-activation (0%, 20%, and 40% of maximum) was systematically induced to elicit muscle stretch reflexes for comparison with stroke patients.
It was observed that elbow flexor stretch reflexes were enhanced when stepwise increases in flexion synergy were induced by shoulder abduction in the paretic arm of stroke patients. Similarly, in the controls, stretch reflexes were found to increase based on the voluntary muscle pre-activation stage. However, flexion synergy induced stretch reflexes in stroke are larger than voluntary muscle pre-activation induced stretch reflexes. This result is different than the finding in a previous study where there is no significant difference between stroke flexion synergy induced stretch reflexes and control voluntary pre-activation induced stretch reflex. This is likely because in the previous study, stroke participants have various muscle tones, and their control group age is younger than stroke group.
The new result suggests that the expression of flexion synergy contributes to hyperactive stretch reflexes; thus, rehabilitation therapies aimed at reducing flexion synergy expression may alleviate spasticity during the everyday use of the arm in stroke patients.

Disclosures: J. Sung: None. **M. Rajabtabar:** None. **B. Mulyana:** None. **H. Peng:** None. **Y. Yang:** None.

Poster

PSTR457: Clinical Stroke, Recovery and Rehabilitation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR457.12/F1

Topic: C.09. Stroke

Support: NIH R01 HD109157
NSF 2401215

Title: Cortical Dynamics of Synergy-induced Hyperactive Stretch Reflex

Authors: *M. RAJABTABAR[1], J. SUNG[1], B. MULYANA[1], R.-T. PENG[1,2], Y. YANG[1,2,3]; [1]Bioengineering, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Clin. Imaging Res. Center, Stephenson Family Clin. Res. Institute, Carle Fndn. Hosp., Urbana, IL; [3]Dept. of Physical Therapy and Human Movement Sciences, Northwestern Univ., Chicago, IL

Abstract: Following a hemiparetic stroke, individuals frequently exhibit flexion synergy—an involuntary integration of the elbow, wrist, and finger flexor muscles—as a symptom of impaired motor control. Previous studies indicate that flexion synergy may also be associated with hyperactive stretch reflex clinically known as spasticity. With a focus on the regulation of activity levels with different amounts of shoulder abduction to induced flexion synergy and enhanced spasticity, this study examines the role of contralesional cortical activity in flexion synergy induced hyperactive stretch reflexes. Furthermore, it investigates the possible influence

of the overexpression of reticulospinal pathways following a stroke on the transcortical reflex linked to the expression of flexion synergy. The initial findings from this investigation included three age-matched controls and two individuals with chronic stroke. For the stroke group, the study used regulated levels of flexion synergy caused by shoulder abduction efforts (0%, 20%, and 40% MVC), and for the control group, voluntary pre-activation of elbow flexors to match the amount of synergy. A robotic device was utilized to stretch the forearm out by extending the elbow at a high pace (peak: 270°/s) at the same time. Different patterns of cortical activity were seen in the EEG recordings made throughout these tasks. Our preliminary results show that stroke participants' Laterality Index (LI) values reduced when the expression of flexion synergy increases with shoulder abduction loads indicating an increased recruitment of contralesional cortical sensorimotor areas. This finding highlighted the gradual activation of cortico-reticulospinal circuits during arm lifting tasks contributes to the enhanced synergy and spasticity issues in stroke.

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Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.01/F2

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH/NCCIH R01AT008563

Title: Predicting placebo response in chronic low back pain patients: a machine learning and brain imaging study

Authors: *V. SACCA, A. URSITTI, S. HODGES, M. ZHU, S. REDDY, J. KONG; Massachusetts Gen. Hosp., Boston, MA

Abstract: Aim: Placebo response is a key component of medical practice. Recently, investigators have started to apply brain stimulation methods to enhance placebo response. The aim of this study was to predict the placebo response with and without transcranial direct current stimulation (tDCS) at right dorsal lateral prefrontal cortex (rDLPFC) in chronic low back pain (cLBP) subjects. Methods: 42 cLBP subjects were recruited and randomized to real and sham tDCS. All tDCS was applied at 2 mA for 20 min using the StarStim system for three consecutive days. An expectancy manipulation model was used to enhance the positive expectancy of participants, and placebo analgesia was measured by comparing the heat pain rating difference to inert “lidocaine” cream and neural (control) inert cream applied on the forearms. We then classified participants into two groups (responder and no-responder) based on the pain rating difference between lidocaine and neutral cream spots above or below the median value of the group (in real and sham tDCS group separately). T1 structural MRI was acquired at baseline and

pre-processed using FSL. The mean volume of the grey matter in 112 brain areas (derived from Harvard-Oxford atlases) was extracted. Random Forest (RF) with a 3-fold cross validation was trained to discriminate between responder and no-responder. Feature selection with a T test was applied before the training. Results: In the real tDCS group, t test showed significant differences between responder and no-responder in the right superior frontal gyrus, right occipital fusiform gyrus, left inferior temporal gyrus, right occipital pole, right insular cortex, right parahippocampal gyrus. RF trained with these features reported an AUC of 0.9, sensibility and specificity of 0.77. The most important predictive features of the placebo response were the right superior frontal gyrus and right parahippocampal gyrus. In the sham tDCS group, t test showed significant differences between responder and no-responder in the left lateral occipital cortex, left superior parietal lobule, and right middle temporal gyrus temporooccipital. RF trained on these features achieved AUC of 0.96 (sensibility of 1 and specificity 0.88). The most important features for the classification were the left lateral occipital cortex and right ACC. Discussion and summary: using machine learning algorithm, we found that the grey matter of certain brain regions may predict the individual placebo response with and without tDCS.

Disclosures: V. Sacca: None. **A. Ursitti:** None. **S. Hodges:** None. **M. Zhu:** None. **S. Reddy:** None. **J. Kong:** Other; JK holds equity in two startup companies (MNT, BTT) and a patent on applying neuromodulation, but declares no conflict of interest..

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.02/Web Only

Topic: D.01. Somatosensation – Pain and Itch

Support: Thanks to CONAHCYT for the postdoctoral fellowship, CVU 487025
Research partially funded by the project SIP 20240463 IPN.
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Title: Analysis of blood oxytocin levels via biosensors in male rats during copulatory analgesia

Authors: *C. E. AGUILAR-PÉREZ[1], O. GONZÁLEZ FLORES[2], A. GALVAN-ROSAS[3], V. LOPEZ GAYOU[4], R. DELGADO MACUIL[5];
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Abstract: Oxytocin (OT) is a peptide neurohormone composed of 9 amino acids produced in the hypothalamus. Subsequently, it is transported to the neurohypophysis, where it is stored. Once a stimulus is applied, OT is released into the bloodstream. In male rats, the involvement of both central and peripheral OT in copulatory analgesia, which consists of reducing pain perception during copulation, has been shown. However, the role of peripheral levels of OT during and after copulation are unknown. In the present study, the Vocalization Threshold to Tail Shock (VTTS) was evaluated in sexually experienced rats, in order to determine the pain threshold during the following copulatory steps: the first ejaculatory series (ES1, n=6); after the first ejaculation (PEI1, n=6); during the second ES (ES2, n=6); and after the second ejaculation (PEI2, n=6). Blood plasma was obtained from 3 representative individuals of each group, and OT was determined using a modern biosensor system capable of detecting this biomolecule. For this, the antibody OT was immobilized on a crystalline silicon support. The blood plasma sample was allowed to interact with the biosensor to detect the OT present in the blood plasma samples. Subsequently, detection was performed using Fourier Transform Infrared Spectroscopy coupled with a microscope to sampling in micro infrared mode. In the region of 1600-1700 cm^{-1} corresponding to the amide I group, an increase in absorbance associated to OT presence was observed in the ES1 group compared to the control group (CTL, no copulation), and this increase was greater during PEI1, reaching the higher value. In the ES2 group, the concentration of OT decreased only compared to PEI1. During PEI2, it was observed that the concentration of OT was below (minimum absorbance value) that of the control group. Principal Component Analysis was performed, and a clustering trend among the different groups it was observed, except in the CTL group. This could be due to individual differences. However, these differences tend to cluster according to the behavior phases, which we observe are related to different intensities in copulatory analgesia as well as OT concentrations.

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Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.03/F3

Topic: D.01. Somatosensation – Pain and Itch

Support: Temerty Faculty of Medicine RHSE Entrance Award

Title: Dynamic changes in cortical thickness with surgical response in trigeminal neuralgia patients

Authors: *E. ADHAMIDHIS[1,5], P. SRISAIKAEW[5], J. LI[1,5], J. KIM[5], T. LATYPOV[1,5], A. NOORANI[2], M. HODAIE[3,4];
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Fac. of Medicine, Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [5]Krembil Res. Institute, Toronto Western Hosp., Univ. Hlth. Network, Toronto, ON, Canada

Abstract: Introduction Trigeminal neuralgia (TN) is a chronic neuropathic pain condition characterized by severe, electric shock-like facial pain. Although surgical treatment for TN can be highly effective in providing pain relief, around 20% of patients remain in pain following surgery. The mechanisms underlying the effect of surgical treatment, and why some patients are non-responsive, remain unknown. Developing objective tools to predict surgical outcome in TN can significantly reduce healthcare costs and the physical burden on patients with unsuccessful surgery. Previously, machine learning models using measures of cortical thickness identified fourteen regional predictors of surgical response in TN. Here, we investigate whether these regions are altered following successful pain relief in order to (1) better understand the neural underpinnings of pain relief and (2) explore the potential of these regions as predictors of response. **Methods** Magnetic resonance imaging (MRI) scans were acquired from 119 patients (44 male, 75 female) with classical TN before and after undergoing Gamma Knife Radiosurgery at Toronto Western Hospital. Patients reported their pain levels pre- and post- surgery on a numerical rating scale and were classified as either responders or non-responders, with response defined as a $\geq$ 75% decrease in pain severity. Cortical thickness measurements were extracted via FreeSurfer 7.2, and head size variation was corrected by using the residual method. **Results** Six regions had significant changes ($p < 0.05$) in cortical thickness in surgical responders (n = 92) with both left- and right-sided pain. Most of these regions had an increase in cortical thickness following pain relief, with one region showing a decrease in patients with right-sided pain only. Notably, four of these six regions had been previously identified as the four strongest predictors of surgical response in TN. No significant changes in cortical thickness were observed for any regions in non-responders (n = 27), suggesting that cortical normalization of these regions is associated with pain relief. Within the responder cohort, females more than male TN patients had greater changes in cortical thickness following surgical treatment. Changes in cortical thickness likely reflects modifications of synaptic density, pruning, and myelination of underlying white matter. Our findings identify regions that are differentially impacted by chronic pain and suggest that normalization of these regions is distinctly associated with pain relief.

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Poster

PSTR458: Pain Imaging and Perception

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Program #/Poster #: PSTR458.04/F4

Topic: D.01. Somatosensation – Pain and Itch

Support: RESC - pAInSense
SNSF - MOVE-IT n. 197271

Title: An ai-powered telemonitoring tool for measuring chronic pain in an at-home settings: pAIn-sense

Authors: *A. CIMOLATO[1], N. GOZZI[1], G. AURUCCI[1], J. METZGER[2], A. BELLITTO[3,4], A. MASSONE[4], B. LEGER[5], M. HUBLI[6,2], A. CURT[6,2], S. RASPOPOVIC[1];
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Abstract: Chronic pain is a severe, debilitating condition that significantly impacts the psychological health, functionality, and overall quality of life in individuals with spinal cord injury and amputees. The management of this condition is complicated by an intricated interplay of biological, psychological, and social factors. Indeed, due to the lack of instruments to disentangle these components, the current therapeutic approaches are limited by the administration of nonspecific drugs, and reliance on subjective self-reports for monitoring patients pain relief. This approach results in high healthcare expenses and patient dissatisfaction. Indeed, developing individualized pain management therapies requires a comprehensive understanding of each patient's multifaceted pain perception, including both physical and emotional aspects. To address this, pAIn-sense aims to enhance pain management through a telemonitoring and decision-support system that accurately captures patients' intricate pain experience. By collecting biometric and psychological data via wearable devices and a user-friendly smartphone app, pAIn-sense provides real-time insights into the complex nature of pain. Preliminary findings show high compliance with the proposed technological solution, demonstrating effective user engagement. Additionally, we observed significant correlations between the daily retorted pain levels and both physiological, e.g. sleep quality, and psychological factors, such as anxiety, highlighting even more the multidimensional nature of pain perception. We successfully captured and identified neurophysiological signatures of pain using sensors from the wearable device. Utilizing these features with standard classifiers, we achieved an accuracy of over 75% in classifying pain attacks. These results highlight the potential of our approach to provide reliable pain assessment for clinical support, paving the way for the development of more targeted therapies that address the complex dimensions of pain.

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Poster

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Support: NIH Grant, NIDA, R21DA047673
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Rocky Mountain Mental Illness Research, Education and Clinical Center for Suicide Prevention

Title: Myoinositol concentration in the anterior cingulate cortex mediates the relationship between chronic pain duration and pain embodiment

Authors: *K. K. SHAH, J. MA, P. SUBRAMANIAM, E. MCGLADE, P. F. RENSHAW, D. A. YURGELUN-TODD;
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Abstract: Pain embodiment is a form of maladaptive body awareness where dysfunctional integration of painful sensations into the assessment of bodily states changes how the body experiences pain. While chronic is known to disrupt metabolites such as glutamate and GABA, little work has characterized other important metabolites such as myoinositol. Myoinositol is a metabolite marker of glial proliferation; changes in myoinositol concentrations can be a sign of astrogliosis, which can alter neuronal function. We have previously found that individuals in chronic pain who are at high risk for opioid misuse have a higher tendency to distract themselves from painful sensations. In this study, we hypothesized that the tendency to distract from pain increases the longer a person has lived with chronic pain and that these changes are driven by an inflammatory state in the anterior cingulate cortex (ACC), reflected by myoinositol concentrations. The ACC is a salience network hub and integrates sensory stimuli to direct a response to the most homeostatically relevant ones, such as pain. Participants were 22 adults (11M/11F) with chronic pain for >3 months and free from substance abuse for >60 days (mean age: 33.8 years; mean duration of pain: 9.9 years). Proton MRS data were acquired with a Siemens 3 Tesla magnet. Pain distraction tendency was measured with the Multidimensional Assessment of Interoceptive Awareness. Pearson correlations were used to examine the relationships among pain duration, myoinositol, and pain distraction tendency. We found the duration of chronic pain ($r = -0.57$, $p = 0.008$) and ACC myoinositol concentration ($r = -0.66$, $p = 0.002$) significantly correlated with the tendency not to distract from painful sensations. To assess causal relationships, we ran a mediation model, with ACC myoinositol concentration mediating the association between pain duration and not-distracting score. The model showed a significant indirect effect ($\beta = -0.029$, BootSE = 0.017, BootCI = [-0.069, -0.003]), indicating that ACC myoinositol concentration is a significant mediator. When our mediator was included in the model, pain duration no longer had a significant direct effect on not-distracting score ($\beta = -0.047$, $p = 0.07$), indicating that ACC myoinositol fully mediates the association between pain duration and not-distracting score. These findings suggest that inflammation in the central nervous system increases with chronic pain duration. This exploratory analysis highlights how temporal dynamics of chronic pain conditions may alter pain-processing centers of the brain, leading to increased pain embodiment and poor functional outcomes such as increased risk for opioid misuse.

Disclosures: K.K. Shah: None. **J. Ma:** None. **P. Subramaniam:** None. **E. McGlade:** None. **P.F. Renshaw:** None. **D.A. Yurgelun-Todd:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.06/F6

Topic: D.01. Somatosensation – Pain and Itch

Support: Canada First Research Excellence Fund to BrainsCAN
NSERC Discovery Grant

Title: Claustrum demonstrates cognitive control related functional connectivity during task onsets

Authors: *C. LIU[1], B. W. STEWART[3], Y. YAO[2], D. A. SEMINOWICZ[1];
[1]Med. Biophysics, [2]Univ. of Western Ontario, London, ON, Canada; [3]Univ. of Maryland Sch. of Dent., Baltimore, MD

Abstract: The irregular and sheet-like structure of the claustrum has long prevented optimal sampling of its signal at 3T fMRI. Recent 3T studies demonstrated its functional connectivity with regions involved in cognitive control, its transient activity at the onset of acute painful stimulation and its directional influence on the dorsolateral prefrontal cortex. These findings could be summarized by the Network Instantiation in Cognitive Control (NICC) model, which proposes that the claustrum receives cognitive control signals from frontal regions and synchronizes activities in the nodes of task-positive and negative networks. This on-going study aims to validate the NICC model by examining the functional connectivity of the claustrum with task-positive and negative networks during a thermal stimulation (TS) and a multi-source interference task (MSIT). Seven healthy participants (females = 3) were recruited for a 7T fMRI study. During TS, participants received pseudorandomized blocks of baseline temperature (32^{o}C), warmth (38^{o}C) or noxious heat (mean = 45.7^{o}C) lasting for 15s each. In MSIT, participants had to make a choice among three symbols / numbers at three difficulty levels (baseline, easy and difficult; in blocks). fMRI data were preprocessed with the indirect normalization preprocessing pipeline and denoised by the regression of white matter and CSF timeseries, motion parameters, outlier scans, session and task effects in the CONN toolbox. Small region confound correction was conducted to reduce the partial volume effect from the neighboring insular and putamen regions. ROI-to-ROI correlational analysis shows that, in MSIT, the right claustrum is significantly connected to the right lateral prefrontal cortex during the baseline condition onset, and significantly connected to the left lateral prefrontal cortex and the posterior parietal cortex during the easy condition onset. The left claustrum is significantly connected to the anterior cingulate cortex during the difficult condition onset. No significant connectivity was found during the remaining lengths of the blocks in MSIT, nor during the whole thermal stimulation task. In line with NICC, our results provide early evidence for the engagement of the claustrum with cognitive control regions at task onsets, while further data collection is required for evaluating the role of the claustrum in cognitive control network instantiation during thermal nociception.

Disclosures: C. Liu: None. **B.W. Stewart:** None. **Y. Yao:** None. **D.A. Seminowicz:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.07/F7

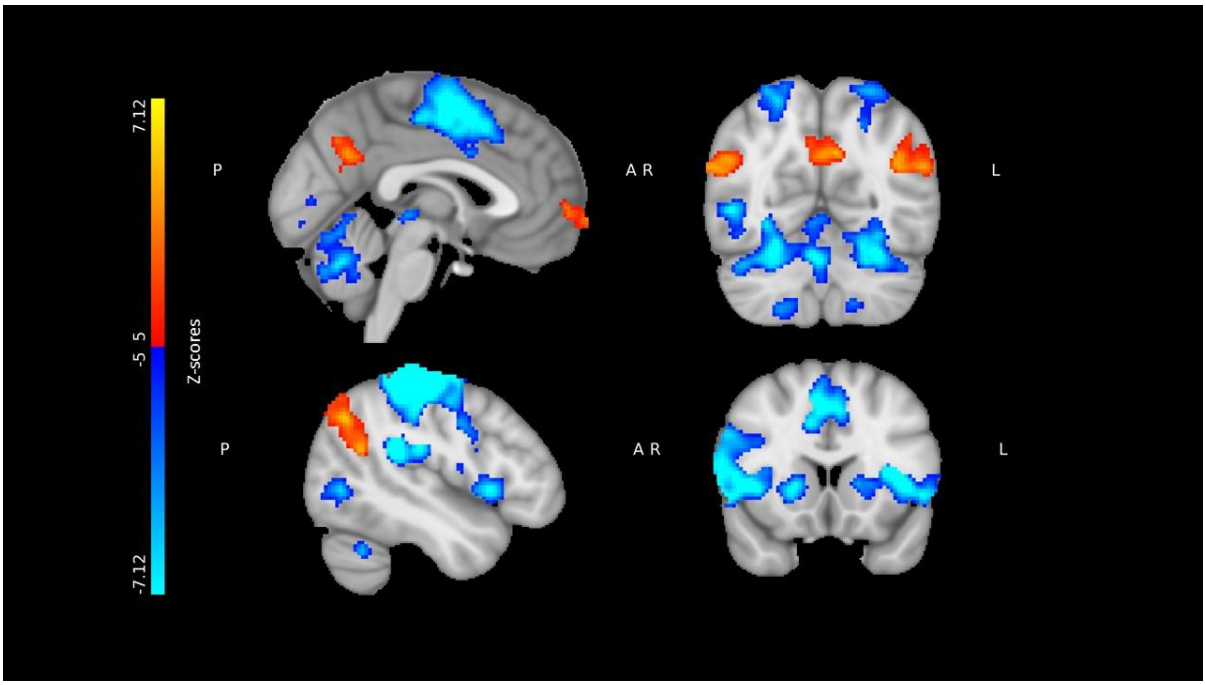
Topic: D.01. Somatosensation – Pain and Itch

Support: R61 NS118651/NS/NINDS NIH HHS/United States

Title: Exploring differential brain responses to pain in high and low impact chronic pain: an fMRI study

Authors: *K. BORNHOFT, Y. WANG, S. MACKEY;
Stanford Univ., Palo Alto, CA

Abstract: Chronic pain presents a significant public health challenge, often associated with functional modifications within the brain. Individuals experiencing high-impact chronic pain (HICP) may exhibit distinct responses to painful stimuli compared to those with low-impact chronic pain (LICP), which may explain differences in pain levels. Our current project characterized the differences in brain activity during painful stimuli between high and low impact chronic pain sufferers. We conducted an investigation involving 120 participants with chronic musculoskeletal pain. Participants were categorized as high-impact (n = 20) and low-impact (n = 100) based on PROMIS Pain Interference T-scores (HICP threshold ≥ 65). Participants (age 19-77, mean = 54), were primarily white (67%) and female (74%). Each participant underwent an fMRI scan while completing a pressure task, where a device applied intermittent pressure (4 kg/in2) to their left thumb across 19 trials during a 6-minute scan session, with each press lasting 3 seconds. Self-reported pain ratings between groups did not differ significantly (two sample T-test, t(118)=1.008, p=0.3157), ensuring that differences in brain activity were not driven by subjective pain experiences. Imaging data was processed using fMRIPrep. Neural responses to the pressure stimuli were modeled using a general linear model and the group level results used a Bonferroni corrected threshold. Our findings reveal that HICP individuals showed heightened activation in the ventromedial prefrontal cortex, angular gyrus, and precuneus compared to the LICP group. Conversely, HICP individuals showed lower activation in the anterior cingulate cortex, insula, sensorimotor cortex, and putamen. These results suggest distinct brain responses to acute pain between high and low impact chronic pain patients, indicative of underlying functional differences within the brain. These insights may contribute to a better understanding of the brain mechanisms underlying chronic pain and inform potential therapeutic strategies targeting the impact of chronic pain.



Disclosures: K. Bornhoft: None. **Y. Wang:** None. **S. Mackey:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.08/F8

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NR020013

Title: Pre-pubertal risk factors for development of dysmenorrhea.

Authors: *M. LENERT;
Michigan Med., Dept. of Anesthesiol., Ann Arbor, MI

Abstract: Dysmenorrhea, pain with menstruation, affects over half of women who menstruate. Many women have severe dysmenorrhea symptoms that interfere with functioning for up to a week each month. Despite this, there is little guidance to predict who will develop severe dysmenorrhea. Underlying pain mechanisms are heterogeneous and may include endometriosis; However, very little is known about pre-pubertal risk factors. In our previous work, we have shown that non-painful somatic symptoms, dysregulated sleep, and attentional issues assessed at age 9-10 are associated with the appearance of multisite pain one year later in the ABCD cohort

(Kaplan et al., 2023). Based on this, our hypothesis was that CNS vulnerabilities for pain are apparent in girls prior to the development of menses and will be significant predictors for future dysmenorrhea. The ABCD study included 11,875 children (9-10 years old) from 21 sites across the United States. All participants provided written informed consent (parents) and informed assent (children). For pubertal status, an average of the child self-report Pubertal Development Scale was calculated. Parents completed the Child Behavior Checklist and the Sleep Disturbance Scale for Children. These analyses focused on pre-menstrual girls who participated in the first data collection wave (age 9-10) and answered questions on the presence and severity of dysmenorrhea at ages 12-13. Using multivariate logistic regression, we tested the association between the presence of pain at age 9-10 (no pain, one pain complaint, two or more pain complaints) and dysmenorrhea at age 12-13. We tested the association between somatic symptoms, sleep, and attentional issues at age 9-10 with subsequent dysmenorrhea at age 12-13. In girls with no pain at age 9-10, more non-painful somatic complaints are associated with dysmenorrhea at ages 12-13 (OR: 1.24, 95% CI: 1.03, 1.49, $p = 0.025$), while attentional issues and sleep problems were not. Two or more pain complaints at age 9-10 were robustly associated with future occurrence of dysmenorrhea (OR:1.36; 95% CI: 1.11, 1.65) and severe dysmenorrhea (intensity $\geq 8/10$; OR: 1.84; 95% CI: 1.35, 2.51; $p<0.01$). These analyses demonstrate that pre-pubertal somatic sensitivity and pain predict both the incidence and severity of dysmenorrhea three years later. The fact that having at least two or more pain complaints was a robust predictor of dysmenorrhea points toward a central sensitization process, as independent pain complaints suggest the development of a broad vulnerability to pain established before puberty. Understanding these risk factors will improve both the diagnosis and treatment of dysmenorrhea in adolescents.

Disclosures: M. Lenert: None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.09/F9

Topic: D.01. Somatosensation – Pain and Itch

Support: 1R01NS12571-01A1
FY2023 Pilot Research Grant Program in Gender Differences and Aging, UTMB
R01NS079166

Title: Development of noninvasive calcium-initiated bioluminescence imaging to measure nociception in mice

Authors: *S. YUAN[1], I. PATRIKEEV[2], J. LIEW[1], M. MOTAMEDI[2], S.-J. TANG[3]; [1]Neurobio., Univ. of Texas Med. Br., Galveston, TX; [2]Ophthalmology and Visual Sci., Univ. of Texas Med. Br., Galveston, TX; [3]Anesthesiol., SUNY Stony Brook Univ., Port Jefferson, NY

Abstract: Objectively measuring pain in laboratory animals is essential for pain research and analgesic development. Although various behavioral tests have been developed to measure evoked pain in animal models; however, measuring spontaneous pain is still a challenge. To address this unmet need, we developed a novel imaging approach to detect spontaneous nociception in pain animal models. We generated a BAC transgenic mouse, named neuronal activity imaging (NAI) mouse, to express Redquorin under the synapsin 1 promoter. In the presence of coelenterazine, the Requorin, which is a fusion protein consisting of aequorin and 2×tdTomato, emits long wavelength bioluminescence from activated neurons that can penetrate tissues for imaging with a Spectrum in vivo imaging (IVIS) system. We have used the NAI mice to image bioluminescence from spinal regions as a surrogate of spontaneous pain induced by capsaicin, HIV-1 gp120, and spinal nerve ligation (SNL). The results show that the Redquorin-emitted bioluminescence is a sensitive optical surrogate to measure spontaneous pain. This approach may offer a potential method to measure spontaneous pain in animal models for basic and translational research.

Disclosures: S. Yuan: None. **I. Patrikeev:** None. **J. Liew:** None. **M. motamedi:** None. **S. Tang:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.10/F10

Topic: D.01. Somatosensation – Pain and Itch

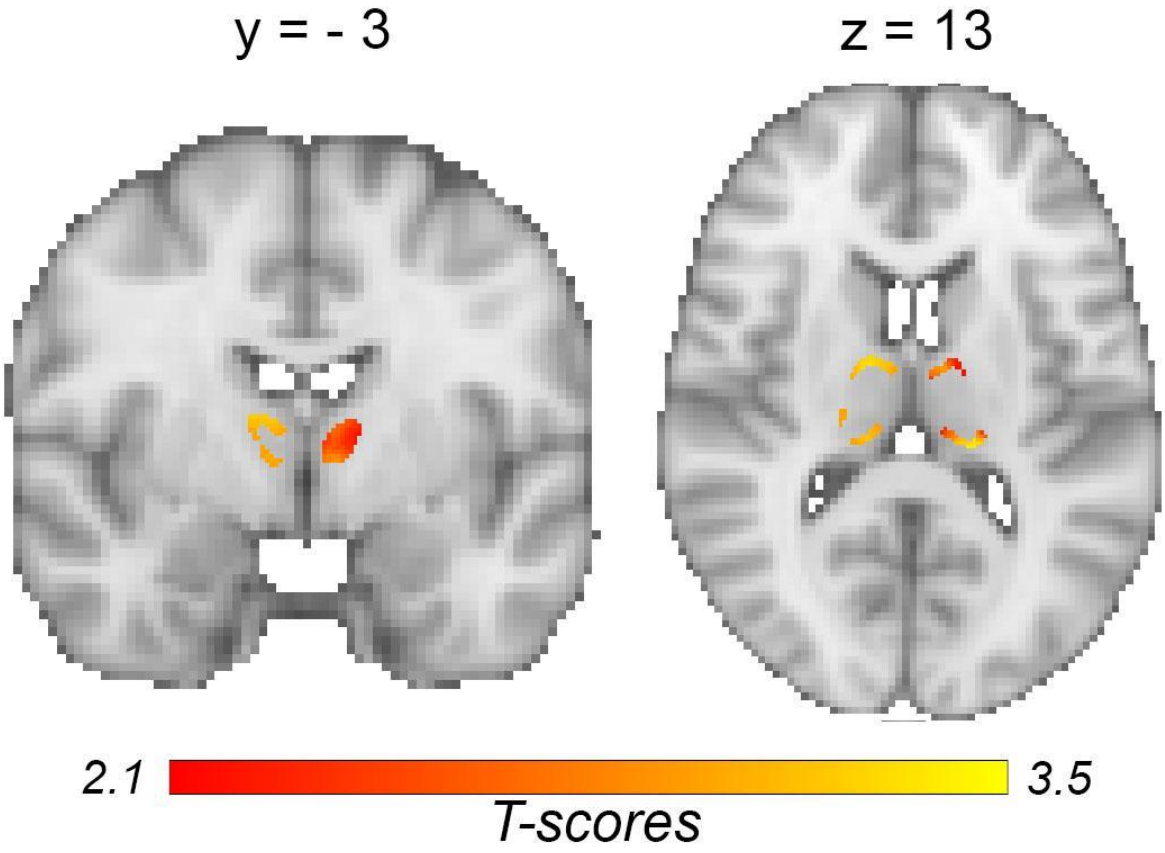
Support: R21 NS118162
R01NS127901

Title: Thalamic plasticity in knee osteoarthritis

Authors: J. NADDOUR[1], N. GRZIBOWSKI[2], J. PAUL[3], ***P. GEHA**[4];
[1]Psychiatry, [2]Physical Med. and Rehabil., [3]Physical Med. and Rehabiliation, Univ. of Rochester Med. Ctr., Rochester, NY; [4]Univ. of Rochester, Rochester, NY

Abstract: Loss of brain gray matter density has been observed in osteoarthritis patients in regions such as the thalamus, insula, and anterior cingulate cortex; interestingly, these changes often normalize following joint replacement. Furthermore, OA patients exhibit reduced volumes in limbic structures like the amygdala and hippocampus. However, structural studies focusing on sub-cortical brain areas in OA are still quite limited. Understanding how sub-cortical limbic structures are altered in OA patients could enhance our understanding of the pathophysiology of chronic pain and aid in developing novel treatments. We studied 25 patients with knee OA and 25 age and sex matched pain-free controls. OA patients reported knee pain of at least 4/10 for at least one year. A T1 MPRAGE was obtained in a 3T PRISMA magnet on all subjects. Patients and pain free controls were not different in age or sex distribution, but patients were heavier than

controls (BMI (kg/m^2) = 26.1 ± 0.8 in controls; 31.5 ± 1.4 in OA patients, $p < 0.01$). Sub-cortical volume and shape were studied using FSL-FIRST and compared between groups using non-parametric permutations with FSL- Randomise after correcting for age, sex, BMI, and signal-to-noise-ratio. There were no significant group differences when comparing the volumes of accumbens, amygdala, hippocampus, or thalamus. However, the 2 groups showed extensive thalamic shape differences (Fig.1) ($p < 0.05$ corrected) where OA patients showed thinning of left and right thalami relative to pain free controls. The thalamic areas affected in patients covered nuclei anatomically connected to prefrontal and temporal lobes respectively. Thalamic changes support the understanding that OA pain is directly linked to peripheral nociceptive input, indicating that it is primarily a bottom-up chronic pain condition. However, the extensive involvement of thalamic nuclei connected to the prefrontal cortex suggests brain plasticity beyond the somatosensory system.



Disclosures: J. Naddour: None. **N. Grzibowski:** None. **J. Paul:** None. **P. Geha:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.11/F11

Topic: D.01. Somatosensation – Pain and Itch

Support: Arthritis Society STAR-21-0000000041
FRQS J1-311042

Title: Diffusion MRI metrics reliability in a longitudinal chronic low back pain cohort

Authors: M.-A. FORTIER[1], P. BAUTIN[1], M. SEAN[1], ***P. TÉTREAULT**[2,3];
[1]Anesthesiol., [2]Anesthesiol. and nuclear medicine and radiobiology, Univ. de Sherbrooke, Sherbrooke, QC, Canada; [3]Med. Imaging Axis CRCHUS, Sherbrooke, QC, Canada

Abstract: Introduction: In recent years, there has been a push to utilize brain imaging to address issues with preventing, classifying and treating chronic pain syndromes such as chronic low back pain (CLBP). Brain diffusion MRI (dMRI) has been used to study white matter microstructure and connectivity across various pathologies and has shown promising findings in CLBP cohorts. However, due to a lack of consensus between study findings, namely because of the high variability in acquisition and processing methods, white matter metrics have yet to become clinically useful to address the different prevention, classification, and treatment issues. Tract based spatial statistics (TBSS), the most used white matter analysis method in chronic pain literature, is known to present different limitations such as registration inaccuracy, assumption that the location of interest is at the tract centers and sensitivity to noise. Therefore, we propose to evaluate and compare diffusion MRI analysis methods reliability using FSL TBSS and tractometry in a longitudinal CLBP cohort. **Method:** We used an observational MRI study comprised of 27 CLBP and 25 healthy control (HC) participants that were scanned 3 times with a 2-month interval between scans. Using a multishell dMRI scanning protocol, DTI and HARDI metrics were computed. FSL's TBSS was used to find voxelwise differences (t-statistic > 2.5) in DTI metrics between CLBP and control cohorts. Only differences between CLBP and HC that were present throughout the 3 visits and with a sufficiently big cluster size (15 voxels) were retained. The tractogram was computed using Tractoflow and the bundles were identified with RecobundleX. This allowed to compare TBSS clusters with tractometry results. **Results:** Fractional anisotropy clusters of difference between controls and CLBPs were identified in the right cingulum, in the right inferior fronto-occipital fasciculus and in the left forceps minor. An average of 403 voxels were clustered across visits and of those, 139 voxels were clustered repeatedly at v1, v2 and v3. To assess the reliability of these clusters, we computed clusters of differences between controls at v1, v2 and v3, and observed only small clusters of 8 voxels maximum in size. **Conclusion:** The aim of this project is to investigate the reliability of dMRI findings across visits and analysis methods. While TBSS shows promising results that seem reproducible across visits, further comparison of cluster size and location with tractometry results will allow confirmation of study robustness. We believe that combining several white matter analysis methods will improve study findings reproducibility and clinical applicability.

Disclosures: M. Fortier: None. **P. Bautin:** None. **M. Sean:** None. **P. Tétreault:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

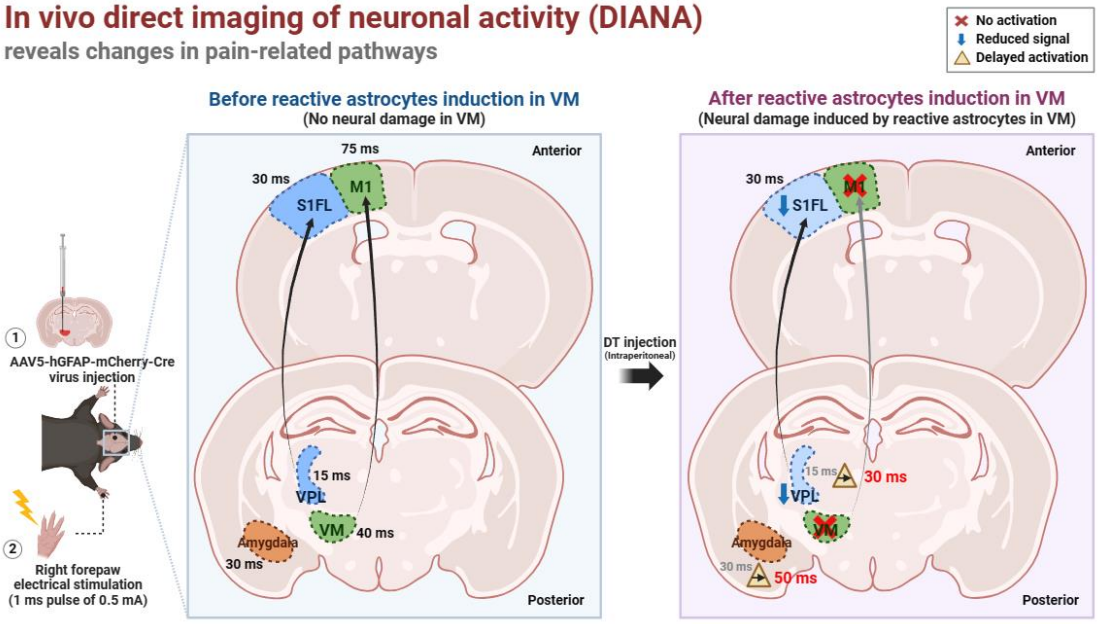
Program #/Poster #: PSTR458.12/F12

Topic: D.01. Somatosensation – Pain and Itch

Title: Direct imaging of neuronal activity functional magnetic resonance imaging reveals spatiotemporal changes in neural circuits in vivo before and after inducing reactive astrocytes in ventromedial thalamic nucleus

Authors: *S. PARK[1], H. SONG[3], S. OH[4], J.-Y. KEUM[1], P. TOI[1], D. KIM[4], H. CHUN[3], J.-Y. PARK[1,2];
[1]Dept. of Intelligent Precision Healthcare Convergence, [2]Dept. of Biomed. Engin., Sungkyunkwan Univ., Suwon, Korea, Republic of; [3]Col. of Pharm., Yonsei Univ., Incheon, Korea, Republic of; [4]Natl. Cancer Ctr., Goyang, Korea, Republic of

Abstract: With the high temporospatial resolution of DIANA fMRI, (Toi et al. Science, 2022) successfully observed whisker somatosensory pathways. It allows to investigate the dynamics of brain activity at millisecond precision. Here we used DIANA fMRI with right forepaw electrical stimulation to observe changes in neural circuits involved in motor and pain networks before and after inducing reactive astrocytes in ventromedial thalamic nucleus (VM), known to play a role in fine motor control and nociceptive signaling. We adopted VM-focal GiD model (VM-fGiD), a Cre-inducible diphtheria toxin receptor transgenic mice (iDTR, n=8) locally injected with AAV-hGFAP-Cre-mCherry virus into VM region. Following intraperitoneal injection of DT, reactive astrocytes was specifically induced in the VM region. DIANA fMRI was performed twice on a 7T animal scanner before and 1 week after DT injection. Electrical stimulation (1 ms pulse of 0.5 mA) was applied to the right forepaw repeatedly every 250 ms. A 1.5-minute rest period was given every 5 trials to reduce neural adaptation. Temporal resolution was 5 ms and in-plane resolution was 0.22 mm. Spatiotemporal DIANA activation maps were created from the peak response time map. Before DT injection, contralateral DIANA activation was observed in VM at 40 ms after stimulation, followed by M1 at 75 ms. However, after inducing reactive astrocytes, no activated voxels were found in VM and M1, showing that reactive astrocytes in VM suppress VM activation and block neural signaling to M1. Changes in pain recognition pathways involving sensory dimension and affective dimension were also observed. For sensory dimension, the contalateral somatosensory pathway was observed showing sequential activation of VPL at 15 ms and S1FL at 30 ms before DT injection. In contrast, after inducing reactive astrocytes, VPL activation occurred at 30 ms with reduced amplitude (0.33% to 0.15%) and S1FL activation occurred at the same 30 ms. For affective dimension, in the amygdala, activation was observed at 30 ms before DT injection, but with a delay of 20 ms after induction.



Disclosures: S. Park: None. **H. Song:** None. **S. Oh:** None. **J. Keum:** None. **P. Toi:** None. **D. Kim:** None. **H. Chun:** None. **J. Park:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.13/F13

Topic: D.01. Somatosensation – Pain and Itch

Title: Spectral EEG-markers of behavioral responsiveness to noxious stimulation in critical care patients

Authors: *V. BUBLITZ[1,2], J. OSTERTAG[3], G. LICHTNER[1], F. VON DINCKLAGE[1];
[1]Dept. of Anesthesia, Critical Care, Emergency and Pain Med., Greifswald Univ. Hosp., Greifswald, Germany; [2]Dept. of Anesthesiol. and Operative Intensive Care Med., Charité - Univ. Hosp. Berlin, Berlin, Germany; [3]Anesthesiol. and Intensive Care, Tech. Univ. of Munich Sch. of Med., Munich, Germany

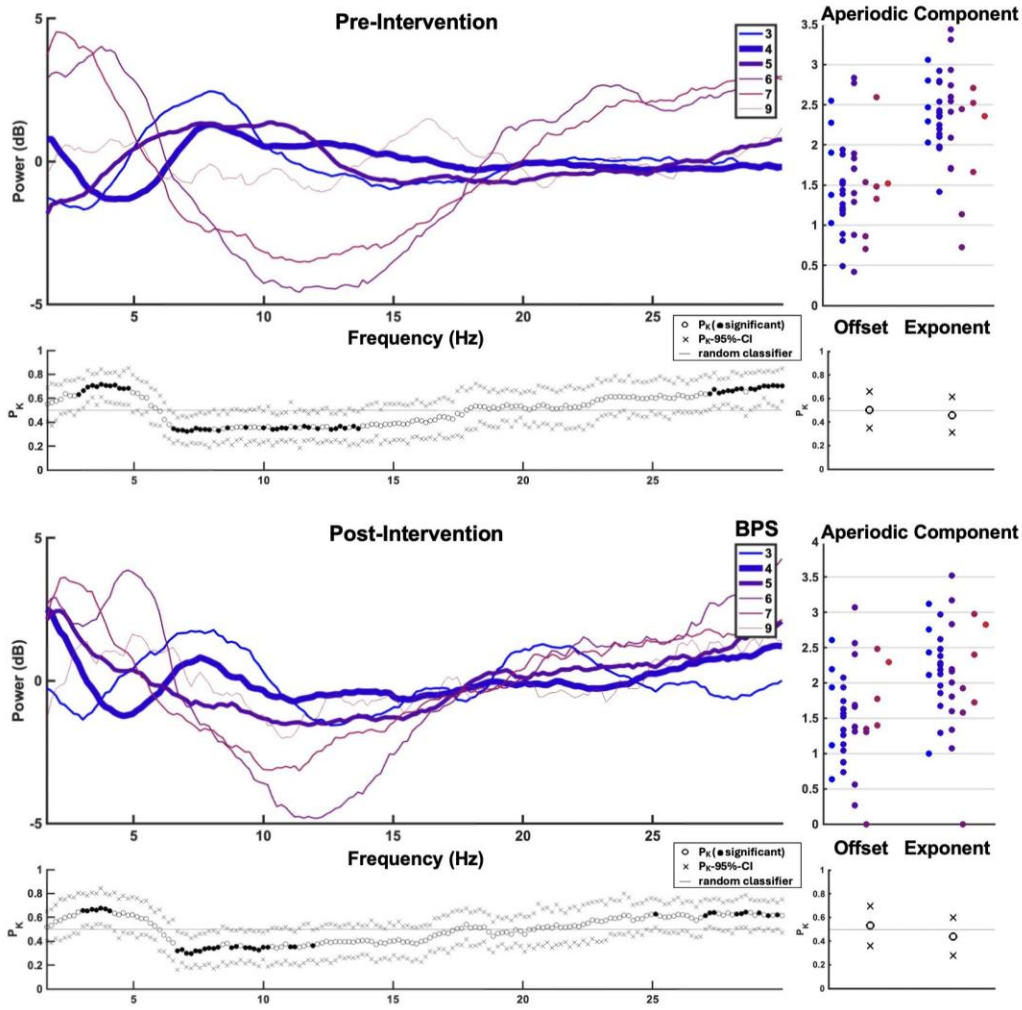
Abstract: Adequate management of analgesia is a crucial aspect in critical care medicine. However, in patients unable to communicate their level of pain, we rely on clinical surrogate markers with limited accuracy. We previously identified spectral EEG correlates that precede and coincide with behavioral responses to painful procedures.
To confirm our previous findings, we analyzed frontal EEG recordings before, during and after endotracheal suctioning in 34 mechanically ventilated patients unable to self-report pain. Behavioral responses to the intervention were assessed using the Behavioral Pain Scale (BPS).

We removed the aperiodic spectral component before testing whether any spectral components precede or coincide with behavioral responses. The remaining spectrum and the parameterized aperiodic component were tested for correlation with the BPS using Prediction Probability (P_K), a polytomous generalization of the area under the receiver operating characteristic for ordinal dependent variables.

Stronger behavioral responses were preceded and coincided with lower activity in the alpha band, higher activity in the delta band and higher activity above 27 Hz. The offset and exponent of the aperiodic component showed no significant correlation.

Our data demonstrates that behavioral responses can be predicted with spectral EEG features, confirming previous findings. Both delta-arousal and a drop in alpha power represent common EEG features signaling excessive nociception in surgical patients under general anesthesia, that can be counteracted by opioids. The ability of these features to predict behavioral responses might be explained by insufficiently treated ongoing tonic nociception caused by the tracheal tube or individual factors. Going forward, these features could help to inform analgetic management by signaling ongoing nociception and thereby allowing preventive measures before noxious procedures.

Previous investigation: https://doi.org/10.1016/j.bja.2022.09.031



Disclosures: V. Bublitz: None. **J. Ostertag:** None. **G. Lichtner:** None. **F. von Dincklage:** None.

Poster

PSTR458: Pain Imaging and Perception

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR458.14/F14

Topic: D.01. Somatosensation – Pain and Itch

Support: R01MH076136

Title: Personalized Imagination-Induced Pain Somatotopy in Nine Individuals

Authors: *M. SUN[1], K. BO[2], B. PETRE[1], T. D. WAGER[3];
[1]Dartmouth Col., HANOVER, NH; [2]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [3]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Pain perception is a complex neural process that involves encoding somatic nociception, aversive emotions, and contextual predictions about the persistence of stimuli causing pain. While previous research has established that the brain encodes pain differently across body sites and stimulation modalities, the specifics of this encoding - such as location, reliability, and individual differences - remain poorly understood. This preregistered fMRI study (https://osf.io/zv4ec) features nine individuals (4 females, 5 males, age 35.63 (11.62)) with deeply-phenotyped whole-brain BOLD activity to thermal pain in eight body sites: left and right face, arms, and legs, as well as chest and abdomen. Individuals underwent ten sessions, each consisting of four runs where painful or non-painful thermal stimuli were intermittently delivered for 13-seconds to one body-site in each run. Within each run, individuals were also intermittently instructed to imagine themselves suffering from intense thermal pain in the same body site as stimulated. Results showed that the imagination of thermal pain produced significant elevations in multiple whole-brain multivoxel heat-pain signatures relative to non-painful thermal stimulation at a group level and a majority (6) of individual subjects. Moreover, multiclass support vector machine revealed robust classification of each single body-site relative to others at both the group and individual level, and somatotopic organization was clear but different in imagined and real, painful and non-painful thermal stimulation. These findings have implications for our understanding of the neural basis of pain perception and its variability among individuals. Specifically, there may be a subset of individuals who can activate regions implicated in specific pain signatures, which may reflect phenotypes relevant for potentiated pain or chronic pain experiences. The degree to which these signatures map onto reported pain exhibited significant body-site and individual variability. There are potentially different body-site-relevant pain patterns per individual, which suggests the need to fine-tune these signatures for individuals.

Disclosures: M. Sun: A. Employment/Salary (full or part-time):; Dartmouth College. **K. Bo:** A. Employment/Salary (full or part-time):; Dartmouth College. **B. Petre:** A. Employment/Salary

(full or part-time):; Dartmouth College. **T.D. Wager:** A. Employment/Salary (full or part-time):; Dartmouth College.

Poster

PSTR459: Olfaction: Peripheral Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.01/F15

Topic: D.03. The Chemical Senses

Support: NIH Grant NS119709

Title: Investigating how hunger shapes navigational decision-making in the Drosophila larva

Authors: E. STAUFFENBERG[1], *D. MATHEW[2];
[1]Univ. of Nevada, Reno, NV; [2]Biol., Univ. of Nevada, Reno, Reno, NV

Abstract: Before a *Drosophila* larva decides to navigate to the left or right, it assesses its odor environment by sweeping its head. Head-sweeping behavior in the larva is orchestrated by the activity of an inhibitory olfactory local neuron, Keystone-LN. Previous research has indicated that Keystone-LN's ability to affect head-sweep behavior and the larva's navigational decisions is sensitive to the larva's hunger state and insulin levels. However, the specific contribution of insulin in mediating hunger-dependent changes in Keystone-LN's function remains unresolved. To address this gap, this research investigates whether insulin is necessary and sufficient for mediating hunger-dependent changes in Keystone-LN's function. First, we optimized Matlab-based algorithms to detect and measure larval head-sweeps during locomotion accurately. Next, leveraging the Gal4/Gal80 gene expression system, we temporally and spatially manipulated insulin signaling levels within Keystone-LN and assessed their impact on larval head-sweep behavior. Our preliminary findings suggest that insulin alone may not be sufficient to mediate the hunger-dependent changes in Keystone-LN's function. Therefore, our ongoing investigations aim to identify additional factors that could mediate hunger-dependent changes in Keystone-LN's function. Unraveling these intricate mechanisms holds promise for advancing our understanding of how hunger influences decision-making behaviors in larval stages, with broader implications for pest management strategies targeting insect vectors such as mosquitoes.

Disclosures: E. Stauffenberg: None. **D. Mathew:** None.

Poster

PSTR459: Olfaction: Peripheral Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.02/F16

Topic: D.03. The Chemical Senses

Support: NIH Grant R01GM148960
NIH Grant P20GM125508

Title: Hyper-olfactory sensing, compensating for vision loss, may evolve through fluid-flow dynamics at the olfactory pit but not the expansion of olfactory receptor gene families.

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Abstract: The evolutionary implications of olfactory abilities and the diversity of olfactory receptors (OR) has garnered strong research attention for decades. A prevailing hypothesis is that the numbers of visual opsin genes and olfactory receptor genes are under a tradeoff. For example, in primates compared to other mammals, increased visual capacity corresponds to a loss of OR genes. We investigate this phenomenon in a single species, *Astyanax mexicanus* (the Mexican tetra), consisting of both blind cave-dwelling (cavefish) and sighted surface (surface fish) populations. Previous studies have found that cavefish have 10^5 times higher olfactory sensitivity to amino acids compared to surface fish, while a few cavefish opsins became pseudogenes. Our comparative genomic analysis between 1 surface and 3 independent cave populations shows that cavefish in fact have slightly smaller numbers of ORs (i.e., 159 vs. 142-148 ORs, respectively) and similar numbers of other chemosensory receptor families compared to surface fish. Thus, we find no support for the OR family expansion for the vision-olfaction tradeoff in *A. mexicanus*. To better understand the physiological and neural mechanisms underpinning the olfactory hypersensitivity of cavefish, we used a combination of electron microscopy, immunohistochemistry, single nucleus RNA sequencing (snRNAseq), and fluid tracing to compare the olfactory epithelia of cave and surface fish. These experiments together revealed (1) reduced numbers and increased sizes of the olfactory lamellae in cavefish, (2) indistinguishable densities of three major classes of olfactory sensory neurons (OSNs) between cavefish and surface fish, (3) response of OSNs to lower concentrations of alanine in cavefish (10^{-10} M) than in surface fish (10^{-6} M), and (4) increased motile cilia coverage on the olfactory lamellae of cavefish. The snRNAseq data also showed an increased proportion of stem cells for OSNs (horizontal basal cells) in cavefish. Moreover, the water flow visualization in the olfactory pits revealed prolonged fluid retention within olfactory pits of cavefish. In conclusion, our findings indicate a surprising mechanism for the evolution of olfactory hypersensitivity of cavefish through a slowed and complex fluid motion in the olfactory pit with few modifications in OSNs.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.03/F17

Topic: D.03. The Chemical Senses

Support: NSF CAREER Grant 2238686
NSF Graduate Research Fellowship

Title: Classification of various human lung cancer cell lines using honeybee olfaction

Authors: *S. MCLANE-SVOBODA[1], A. MCLANE-SVOBODA[1], S. W. SANCHEZ[1], M. PARNAS[1], E. COX[1], A. TUNDO[1], C. CONTAG[1], D. SAHA[1,2];
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Abstract: Molecular signatures, comprised of volatile organic compounds (VOCs), are expelled through breath and bodily fluids, providing insights into health. Pathological processes (e.g., lung cancer) emit various concentrations of VOCs through metabolic pathways as byproducts. Lung cancer progression alters metabolic processes within a cell, thus modifying the volatile profile of the emitted VOC mixture (e.g., exhaled breath). These diseased cells exhibit distinct morphologic and metabolic characteristics compared to healthy cells. Changes in cellular growth and energy production metabolites distinguish lung cancer's volatile profile compared to healthy lung fibroblasts. Chemical sensing utilizing VOC detection has been examined using gas chromatography-mass spectrometry and electric noses; however, despite these devices being specific and sensitive, they do not detect a wide range of volatiles at low concentrations. Alternatively, highly efficient biological chemical sensing pathways have evolved across the animal kingdom. Specifically, honeybees can detect odorant concentrations from various distances, showing precise, sensitive chemosensory capabilities and enabling the identification of diverse volatile chemicals. Honeybee antennae consist of olfactory receptor neurons transmitting odor-evoked neural responses to the antennal lobe (AL). Honeybees employ their AL neural computation to produce odor-specific spatiotemporal coding schemes to identify diverse odorants at various concentrations. Here we employed biological olfaction in human lung cancer cell line detection by conducting *in-vivo* extracellular neural recordings from honeybee ALs and analyzing distinct VOC mixture-evoked neural spiking responses. Recordings were conducted using a multi-channel flexible electrode inserted into the AL. The study focused on classifying specific lung cancer cell lines. Two types of lung cancer, non-small cell (NSCLC) and small cell (SCLC) were examined. VOCs present in the headspace of each cancer flask were presented to the honeybee antennae while neural recordings were made from AL neurons. We achieved a high classification success rate for all the stimuli tested, which included seven cell lines: four NSCLC, two SCLC, a healthy lung fibroblast control, and a media control. Our results indicate the honeybee olfactory system can be employed to identify lung cancer biomarkers and distinguish between various types of human lung cancer cell lines.

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Poster

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Topic: D.03. The Chemical Senses

Support: NSF Grant 2323240
NSF Graduate Research Fellowship

Title: Quantifying associative learning-induced changes in population neural responses in an insect brain.

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Abstract: Throughout biology, associative learning displays diverse capacities, with several systems utilizing this mechanism to generalize learned stimuli from only a few presentations, a skill most engineered systems lack to date. Locusts are one organism with great ability to learn, associating specific learned odors with food and generalizing the information over different stimulus presentation conditions. Locusts detect odors through olfactory receptor neurons in their antennae that transmit electrical signals to the antennal lobe (AL) where information is processed by a dense network of excitatory (projection) and inhibitory (local) neurons. Spatiotemporal spiking responses of projection neurons within the AL are altered in response to odor identity and concentration. Here, we utilize the locust olfactory system to study neural computations underlying learning and subsequent behavioral outcomes. Understanding the computational mechanisms of associative learning allows us to replicate biology's capability to generalize information within engineered machine learning frameworks.
We employed a new minimally invasive surgical technique where locusts underwent surgery to expose a small window over the AL. This procedure ensured that locusts retained functionality of their mouth and palps for behavioral training, while an electrode was inserted into the AL. Three odors were presented to the locusts, a target odor, a chemically similar odor to the target, and a chemically distinct odor. Odor-evoked baseline activity was recorded by presenting odors to the locust antennae before training. Locusts then were trained to a specific odor by associating sucrose solution reward with the target odor and then put through the odor protocol once more. All three odors were introduced to the locust antennae separately to record individual responses, then the trained odor was presented immediately before and after the untrained odors. This procedure was repeated on the same locust at the same neural recording location before and after associative learning. We aimed to address whether the locust generalizes its learned association of the trained odor when presented with a chemically similar odor and whether presenting a distracting odor in sequence with the trained odor changes the response. From AL neural recordings and palp-opening responses, we aim to identify learning-induced changes in in-vivo neuronal activity and how that influenced locust behavior. The long-term goal of this study is to

implement associative learning-induced neuronal changes and constraints within machine learning framework to further define fundamental associative learning principles.

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Poster

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Topic: D.03. The Chemical Senses

Support: NSF CAREER to DS
MSU Startup to DS
NSF GRF to AMS

Title: Detecting infectious bacterial biofilms using the locust olfactory system

Authors: *M. PARNAS[1], E. COX[2], M. SHAHAB[1], A. MCLANE-SVOBODA[1], S. MCLANE-SVOBODA[1], C. STOUT[3], J. HARDY[1], D. SAHA[1,3];
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Abstract: The treatment of bacterial infections is greatly hindered by the formation of biofilms. Biofilms occur when bacteria secrete an extra-cellular matrix thereby creating a non-mobile colony on surfaces. When bacteria form biofilms they become more resistant to the host immune system and anti-microbial drugs. Biofilm infections occur in implants, wounds, surgical sites and in the lung, where they can persist and resist treatment. It is therefore important to be able to differentiate bacteria in biofilms from free-swimming (planktonic) bacteria. Metabolic changes occur as bacteria shift from planktonic to biofilm, which results in changes to the volatile organic compounds (VOCs) produced by the bacteria, providing a means of identifying biofilms. Here, we used the biological VOC sensing system of locusts to differentiate two medically relevant bacterial species (*Pseudomonas aeruginosa* and *Staphylococcus aureus*) and to identify planktonic and biofilm growth patterns. *P. aeruginosa* and *S. aureus* have become increasingly drug resistant with multi-drug resistant strains causing more serious infections and re-infections, especially within the respiratory tract. Identifying biofilms using VOCs will provide a new tool for analysis and improve the treatment of bacterial infections.
Locusts have evolved incredibly sensitive olfactory systems with the ability to detect VOCs at parts per trillion concentrations, on par with dogs. Neurons within locust antennae interact with molecules in the surrounding environment to transform signals from this chemical milieu into electrical impulses that are then processed by the antennal lobe (AL) neural network consisting of excitatory projection neurons and inhibitory local neurons. We presented odors from cultured *P. aeruginosa* and *S. aureus* to locust antennae while simultaneously conducting *in vivo* extracellular electrophysiology recordings from the projection neurons in the AL. We then

employed biological neural computation schemes to decode the odor-evoked neural responses. Our results demonstrate that we can use this biological gas sensor to detect and discriminate bacterial species and biofilm formations based on the 'smell' of the emitted VOC profile. Using population neural responses and a simple linear classifier we achieved 100% accuracy for stimulus classification. Furthermore, using hierarchical clustering, we show that the locust neural responses are more dissimilar across bacterial species than across metabolic states within a bacterial species. This biological VOC sensing approach has potential application for detecting dangerous biofilms.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Topic: D.03. The Chemical Senses

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Title: Inferring Network Structure from Neural Activity in a Biologically-Constrained Model of the Insect Olfactory System

Authors: *S. JOSHI[1], G. NAVAS[2], A. MCLANE-SVOBODA[3], S. W. SANCHEZ[3], D. SAHA[3], M. V. BAZHENOV[4];
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Abstract: Olfactory processing in insects relies on the complex circuitry of the antennal lobe (AL), where excitatory projection neurons (PNs) and inhibitory local neurons (LNs) interact to shape odor representations. The AL exhibits intricate dynamics, with PNs and LNs displaying diverse temporal response patterns. While existing computational models of the AL provide valuable insights, they often rely on hand-tuned parameters and do not fully leverage the wealth of available *in vivo* data. In this study, we construct a biologically grounded continuous rate RNN model of the locust AL, consisting of 820 PNs and 300 LNs. The model is trained using backpropagation through time to minimize the reconstruction error between the firing rates of the RNN units and *in vivo* PNs, while optimizing input weights, recurrent weights, and membrane time constants. The trained RNN model successfully recreated PN firing rates and exhibited distinct temporal dynamics, with some units responding at the onset of odors, some at the offset, and a few at both onset and offset, matching experimentally observed patterns. Trained connection probabilities between PNs and LNs were consistent with values estimated empirically. When non-zero PN-PN connections were allowed, the training process eliminated

the vast majority of them, took longer to converge, and resulted in a worse fit to data. This aligns with the experimentally documented absence of PN-PN connections in the locust AL. The trained time constants for both PNs and LNs exhibited a distribution with mostly low values and a small number of units with high values. Most PNs responded with time constants of ~30ms while most LNs responded with time constants of ~70ms, partially attributed to LNs generating slower Ca^{2+} spikelets instead of Na^{+} spikes in locusts. Splitting PNs by time constants uncovered distinct activity patterns: low time constant PNs respond at odor onset, while high time constant PNs respond with a delay or at odor offset. As the model lacks explicit synaptic time constants, unit time constants may integrate fast and slow synaptic scales, predicting high time constant units (400-500ms) accounting for slow inhibitory synapses in the locust AL. Our biologically constrained locust AL RNN model captures diverse PN and LN activity patterns and provides insights into the functional roles of neuron types and synaptic connectivity in olfactory processing dynamics. This study demonstrates the effectiveness of using RNNs to investigate biological systems, generating testable predictions for future experimental studies.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Topic: D.03. The Chemical Senses

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Title: Single cell transcriptomics of vomeronasal neuroepithelium reveals a differential endoplasmic reticulum environment amongst neuronal subtypes

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Abstract: Specialized chemosensory signals elicit innate social behaviors in individuals of several vertebrate species, a process that is mediated via the accessory olfactory system (AOS). The AOS comprising the peripheral sensory vomeronasal organ has evolved elaborate molecular and cellular mechanisms to detect chemo signals. To gain insight into the cell types, developmental gene expression patterns and functional differences amongst neurons, we performed single cell transcriptomics of the mouse vomeronasal sensory epithelium. Our analysis reveals diverse cell types with gene expression patterns specific to each, which we made available as a searchable web resource accessed from www.scvnoexplorer.com. Pseudo-time developmental analysis indicates that neurons originating from common progenitors diverge in

their gene expression during maturation with transient and persistent transcription factor expression at critical branch points. Comparative analysis across two of the major neuronal subtypes that express divergent GPCR families and the G-protein subunits Gnai2 or Gnao1, reveals significantly higher expression of endoplasmic reticulum (ER) associated genes within Gnao1 neurons. In addition, differences in ER content and prevalence of cubic membrane ER ultrastructure revealed by electron microscopy, indicate fundamental differences in ER function.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Topic: D.03. The Chemical Senses

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Title: Rapid odorant metabolism explains inhalation-linked dynamics and chemical tuning of glomerular odor representations in the mouse olfactory bulb

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Abstract: In the mammalian olfactory system, odorants evoke distinct inhalation-linked temporal patterns of activity, yet how these patterns arise and how they impact odor information coding remain unclear. We addressed this using two-photon imaging from the olfactory bulb (OB) of awake, head-fixed mice expressing calcium (GCaMP6/8) or glutamate reporters (iGluSnFR) in olfactory sensory neurons (OSNs) or mitral/tufted (MT) cells. We first tested the hypothesis that inhalation-linked response latencies reflect relative odorant sensitivity, such that latency patterns across glomeruli are concentration-invariant. We built on recent work establishing ‘primary’ glomeruli for particular odorants (Burton et al., doi: 10.7554/eLife.80470) and characterized response dynamics across concentrations. Increasing odorant concentration recruited activation in ‘non-primary’ glomeruli. Initial response latencies for a glomerulus were only weakly correlated with relative sensitivity, and even this weak correlation did not persist across successive inhalations. Instead, differences in inhalation-linked response dynamics were well-predicted by a combination of odorant chemistry and glomerular location. In particular, glomeruli in the class I OSN domain showed fast responses to carboxylic acids and slower, weakly inhalation-linked responses to their corresponding esters, aldehydes and alcohols, while ester-sensitive glomeruli in the class II domain responded rapidly. Latency patterns persisted in the somata of tufted and mitral cells innervating each glomerulus, suggesting that slow activation of OSN input drives slow activation, rather than suppression, of MT cells. We next considered an alternate hypothesis in which longer-latency responses reflect the rapid (sub-sniff) conversion of

certain inhaled odorants into secondary odorants by xenobiotic enzymes in the nasal epithelium. This model explains the distinct temporal patterns of glomerular activation observed across the OB surface, as well as the apparently-complex tuning of glomeruli to odorants with diverse structures. Overall, these results suggest that perireceptor processes - rather than relative sensitivity - are the strongest determinants of the dynamics of glomerular odor representations, and that these dynamics persist at the level of OB output. They also suggest a novel role for inhalation-linked timing in odor coding, which is to disambiguate inhaled odorants arising from external sources from those generated by processes internal to the animal itself.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Topic: D.03. The Chemical Senses

Support: 1R01NS111673-01 (NINDS, NIH)
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Title: Mapping odorant receptors to glomeruli and their odor responses in the mouse olfactory bulb

Authors: *D. ALBEANU[1], C. SOITU[2], W. G. BAST[3], Z. DAWOOD[1], A. BECALICK[4], D. E. HERNANDEZ TREJO[3], P. ZNAMENSKIY[4], A. M. ZADOR[5], A. KOULAKOV[6];
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Abstract: In mammals, odorants are sensed by the olfactory sensory neurons (OSNs) of the olfactory epithelium. Each OSN expresses one member of the odorant receptor (OR) gene family, approximately 1,100 in mouse. OSNs expressing the same OR gene converge to discrete spherical structures on the surface of the olfactory bulb (OB), called glomeruli. The spatiotemporal pattern of glomerular activation is thought to represent information about odorants. A comprehensive convergence map of OSNs expressing different ORs could help discover the algorithms that relate the odor space to the underlying neural circuits and to olfactory perception. Detection of OR gene expression *in-situ* has been successfully demonstrated recently. While these studies provided impactful look-up tables for the location of specific subsets ORs on the bulb surface, several technical constraints in spatial resolution or throughput have limited our ability to accurately associate a glomerulus with one or several ORs. Here, we use a high throughput *in situ* sequencing method (BARseq) to detect a large fraction of ORs at sub-glomerular resolution in 20 µm thick olfactory bulb slices. We designed *in situ*

sequencing padlocks (5-10 per OR to increase detection) aimed to specifically target all OR transcripts. We performed BARseq on three brains and detected ~400 ORs which form tight spatial clusters within the glomerular layer of individual bulb slices. The number of OR transcripts detected *in situ* was significantly correlated with OR expression levels in bulk olfactory bulb RNAseq data. This approach enables us to construct a high-resolution OR/glomerular map of the OB and re-visit basic anatomical questions such as: 1. How reproducible is the glomerular odorant receptor map across animals? 2. To what extent there is mixing of different OR types in individual glomeruli? 3. What is the relationship between the glomerular position of an OR on the bulb surface and its sequence? This strategy enables us to combine *in situ* OR sequencing with *in-vivo* imaging of their responses to large odorant panels, and to barcoding of mitral and tufted cell projections to downstream target regions.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Title: Norepinephrine modulation of intergenerational stress-induced olfactory plasticity

Authors: *T. ARZUA[1], A. CARDEIRO[2], D.-L. FERGUSON[2], B. R. MCRAE[2], A. VINA-ALBARRACIN[2], B. J. MARLIN[2];
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Abstract: Essential for the survival of any species, humans included, is the ability to detect and respond to threats efficiently. Nevertheless, the traumas and stress of our current world can change these circuits, potentially leading to post-traumatic stress disorder, panic disorder, and generalized anxiety. Using the mouse's olfactory system, work from our lab has shown that fear conditioning increases the number of odor-specific olfactory receptors both in conditioned parents and their naïve offspring when compared to control groups. We hypothesize that norepinephrine (NE), produced by the the locus coeruleus (LC), is a key modulator of these morphological changes. NE is crucial in regulating brain-wide responses to stress, including influencing sensory plasticity. To address the gaps in the knowledge of how traumatic experiences are encoded in the brain, this study seeks to understand how NE can modulate olfactory plasticity caused by stress.

To fully dissect these circuits, we have used a combination of olfactory fear conditioning, tissue clearing, fiber photometry, and optogenetics. Fiber photometry showed increased LC activity both during conditioning, as well as in a re-exposure to the conditioning odor. Interestingly, female mice had a significantly higher response to each individual presentation of the unconditioned stimulus (0.2mA, 200 ms foot shock). We have also confirmed NE release in the olfactory bulb during conditioning, via GRABNE sensors. To confirm if LC modulation is necessary and sufficient to induce olfactory plasticity, we have optogenetically stimulated and silenced LC activity and subsequently determined the number of odor-specific olfactory receptors - in parents and in their naïve offspring. Together, this work will provide insights into how modulation by a structure deep in the brainstem can affect how stressful experiences are processed and represented in the brain. From a broader societal perspective, this will be a step toward a more comprehensive and specific response to the ongoing mental health crisis.

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Poster

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Title: Determining the molecular mechanisms of stress-induced bias in olfactory neuron identity

Authors: *B. STECKY[1], A. CARDEIRO[1], S. LOMVARDAS[2], B. J. MARLIN[3];
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Abstract: Human history gives us myriad examples of intergenerational inheritance of the experience of stress (Heijmans et al., 2008; Yehuda et al., 2016; Schmitz and Duque 2022). Recently these population-wide examples have been supported with animal model data that suggest stress-induced somatic changes can be inherited across generations (Carone et al., 2010; Dias and Ressler, 2014). Using the mouse model, the Marlin lab has found that pairing an odor

with a mild foot shock - a behavioral paradigm called olfactory fear conditioning - induces an upregulation in the number of olfactory sensory neurons (OSNs) that respond to the paired odor. Strikingly, this phenotype has been demonstrated in both conditioned mice and their unconditioned progeny (Liff et al., 2023). Given the semi-stochasticity of olfactory receptor choice during OSN differentiation (Monahan and Lomvardas 2015), how does odor-shock pairing disrupt this stochastic process to produce a bias in the distribution of OSN identity? I aim to identify molecular mechanisms of this stress-induced bias in neuronal identity. After olfactory fear conditioning with the P2 odor ligand, I perform bulk RNA-sequencing on isolated P2-expressing OSNs ("GFP+ cells") with the goal of determining the precise nature of differential gene expression between odor-shock paired mice and the odor-shock unpaired control group (n = 5 animals per condition). Using a generalized linear model to compare GFP+ cells between the two groups (DESeq2, Love et al., 2014), I observe differential regulation in a suite of genes involved in the unfolded protein response (UPR). A cellular signaling pathway of many functions, the UPR becomes transiently active at the precise moment of olfactory receptor choice (Dalton et al., 2013). Using gene set enrichment analysis to parse the many UPR subprocesses, I find significant negative enrichment of endoplasmic reticulum (ER) stress response and associated apoptotic pathways in the paired group (normalized enrichment score < -1.5, p-value < 0.05). These data suggest that odor-shock pairing reduces ER stress and apoptosis in odor-activated neurons, hinting at a potential mechanism of stress-induced bias in neuronal identity. These findings have profound implications in helping us understand how the olfactory system integrates salient environmental information and how stressful experiences can regulate gene expression and even cellular identity in a heritable manner.

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Poster

PSTR459: Olfaction: Peripheral Mechanisms

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Topic: D.03. The Chemical Senses

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CONAHCYT A1S8948

Title: Olfactory dysfunction in chronic kidney disease: from a mouse model to human patients

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Abstract: Chronic kidney disease (CKD) is a global health problem with increasing prevalence in Mexico, with diabetes and hypertension as the most common causes. CKD is defined by the gradual loss of kidney function as demonstrated by a deficiency in the glomerular filtration rate. Alterations in the sense of smell are frequently experienced by CKD patients, but much is still unknown regarding the pathophysiology of the olfactory function in this disease. Such olfactory deficiencies are not usually perceived and can affect taste perception and food ingestion, altering the patient´s quality of life. In the present work, we evaluated a group of 36 CKD-diagnosed patients and 40 healthy subjects (control group) within the 18-60-year-old range. Olfactory alterations were evaluated by a series of tests aimed at determining their ability to discriminate, identify, and memorize a set of odors. Additionally, to determine the alteration of smell in the progression of the disease, C57BL/6J female mice were treated with adenine (50 mg/kg PO via intragastric cannula, n=10) for 4 weeks as a kidney disease (KD) model. In the mice, we evaluated their ability to detect and locate the food source (Buried Food Test -BFT-) and the capacity to differentiate odors (Habituation/Dishabituation Test -HDT-). Routine biochemical and metabolic parameters of the disease were determined in both CKD patients and KD mice. Serum urea and creatinine were significantly elevated in CKD patients as well as in the KD mice. The renal damage was confirmed in the KD mice by histology of kidney sections showing augmented tubular dilation and luminal necrotic debris accumulation. Regarding the olfactory assessment in CKD patients, odor identification and discrimination were significantly reduced compared to healthy subjects. However, no deficits were found with the memory test. In the KD model, olfactory capacity alteration in the mice was present after the second week of the adenine treatment. The BFT in KD mice showed alterations in the detection of volatile cues by displaying higher latencies to find the hidden food. Also, the capacity to discriminate odors was compromised in KD mice as shown by the HDT. Overall, our results in CKD patients and the KD mouse model indicate that kidney disease promotes olfactory alterations. Specifically, our results in KD mice suggest that the olfactory deficiencies might begin early in the development of the disease. The present evaluation of CKD patients represents the first study in Mexico showing the compromised olfactory capacity in these patients and highlights the relevance and the need for further studies, both basic and clinical, regarding the sense of olfaction in this disease.

Disclosures: R. Corona: None. **V. Viñuela-Berni:** None. **M. Carbajo-Mata:** None. **I. Jover:** None. **L. Robles-Osorio:** None. **E. Sabath:** None. **T. Morales:** None.

Poster

PSTR459: Olfaction: Peripheral Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.13/F28

Topic: D.03. The Chemical Senses

Support: Michigan Space Grant Consortium
Hope College

Title: Effects of acute hypoxic exposure in the olfactory system of adult zebrafish

Authors: *K. DEMANN, S. DEWITT, E. CALVO-OCHOA;
Neurosci., Hope Col., Holland, MI

Abstract: Hypoxia, the lack of sufficient oxygen in tissues to sustain bodily functions, has a deleterious effect on brain health. Additionally, decreased dissolved oxygen levels in aquatic environments occur as a result of climate change. Zebrafish offer an excellent model to study hypoxia due to extensive neuroplasticity and injury-induced cell proliferation, which allows them to recover lost function in the central nervous system (CNS). In particular, the olfactory system of zebrafish exhibits remarkable plasticity and regenerative properties. Moreover, its architecture is similar to those of other taxa, including mammals, which makes it an ideal model to study olfactory dysfunction and recovery. Olfactory sensory neurons (OSN) in the olfactory epithelium (OE) detect and transmit odorant information to the olfactory bulb (OB) which discriminates odorants and relays the information further to the brain. In this study, we establish a new paradigm of acute hypoxic exposure in zebrafish to uncover the effects of oxygen deprivation on the olfactory system's structure and function. To induce hypoxia, zebrafish were placed in a tank with hypoxic levels of 0.6-0.8 mg/mL dissolved O2 (DO) for 15 minutes and then recovered for 1-day post hypoxia (1 dph). We hypothesized that hypoxia is associated with a loss of smell due to abnormalities in the olfactory epithelium. To study this, we assessed olfactory-mediated responses to cadaverine, an odorant that elicits alarm responses in zebrafish, characterized by freezing, sinking, and decreased exploration of the tank. To assess olfactory epithelium's integrity we stained for active mitochondrial dehydrogenase activity to study mitochondrial function and performed immunohistochemistry assays to assess structural degeneration and neuroinflammation in the olfactory system. We also measured OSN activity by labeling with c-Fos, a marker of neural activity. In addition, we utilized Alcian Blue stainings of the OE to visualize the mucus layer and the structure of mucus-producing Bowman Glands. We observed reduced responses to cadaverine in the hypoxic group, indicative of olfactory loss. We also found mitochondrial activity reduction, increased astrocyte activation, and apoptosis markers in the olfactory bulb. Interestingly, we found changes in the mucus layer in the OE as well as epithelial swelling along with changes in OSN activation. Collectively, our results characterize olfactory loss associated with degeneration of the olfactory system caused by hypoxia. This work provides insights into hypoxia's impact on olfaction, specifically olfactory morphology and function.

Disclosures: K. DeMann: None. **S. DeWitt:** None. **E. Calvo-Ochoa:** None.

Poster

PSTR459: Olfaction: Peripheral Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR459.14/F29

Topic: D.03. The Chemical Senses

Support: 5T32NS007433
R01DC018516

Title: Immature olfactory sensory neurons provide complementary odor information

Authors: *J. D. GREGORY[1], R. S. HERZOG[1], C. E. CHEETHAM[2];
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Abstract: To better develop strategies to repair damaged brain areas via stem cell-derived neurons, it is imperative to understand how endogenously generated neurons can functionally integrate into existing neural circuitry. The mammalian olfactory bulb (OB) is a valuable model to study the functional integration of adult-born neurons in both the healthy and regenerating brain. Adult-born olfactory sensory neurons (OSNs) go through immature and mature developmental stages as they wire into the OB. We have shown that immature OSNs provide odor input to the mouse OB and exhibit graded responses across a wider odorant concentration rage than mature OSNs. Therefore, our hypothesis is that immature OSNs provide distinct odor information that complements the input from mature OSNs. To test this hypothesis, we employed Gγ8-tTA;tetO-hM4Di transgenic mice to chemogenetically silence immature OSNs via clozapine N-oxide (CNO) mediated activation of the inhibitory DREADD hM4Di. We first validated both DREADD expression and the efficacy of CNO in silencing immature OSNs. Mice then completed both olfactory habituation/dishabituation and buried food tests to determine the effect of silencing immature OSNs on odor-guided behaviors. From these tests, it appears that immature OSN silencing impairs mice's ability to both detect and discriminate odors. Finally, to determine the functional contribution of immature OSNs in olfaction, we imaged odor-evoked responses in GCaMP6s-expressing mitral cells via in vivo 2-photon microscopy before and after hM4Di-mediated silencing. Here we see that silencing immature OSNs reduces odor-evoked calcium responses in the OB to a variety of odorants. Together, these experiments suggest that immature OSNs provide information complementary to that provided by mature OSN activity, thus suggesting that immature OSNs make an important contribution to odor processing in the healthy OB.

Disclosures: J.D. Gregory: None. **R.S. Herzog:** None. **C.E. Cheetham:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.01/F30

Topic: D.05. Auditory and Vestibular Systems

Support: DoD-ARL

Title: Visual Modifications on Auditory Neurons in Behaving Non-human Primates

Authors: *H. CAI[1], Y. E. COHEN[2];
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Abstract: Because we live in a multisensory environment, it is reasonable to speculate that our brain has evolved to preferentially take advantage of multisensory information. However, despite a large literature examining multisensory processing, we still do not have a full understanding of how cortical activity (e.g., in the primary auditory cortex [A1]) contributes to multisensory perception. Here, we recorded A1 neural activity in non-human primates while they performed an ethologically relevant multisensory detection task that utilized monkey vocalizations and a video of a vocalizing monkey. We manipulated task difficulty by varying the signal-to-noise ratio (SNR) between an auditory target stimulus (i.e., a monkey "coo" vocalization) and a background noisy "chorus" of monkey vocalizations. We found that a temporally and contextually congruent video of a vocalizing monkey improved the monkeys' ability to detect the target vocalization. Our analyses of A1 activity indicated that 1) it was modulated more by visual stimuli in lower SNR conditions than in higher SNR conditions; 2) visual stimuli improved the capacity of linear classifiers to decode target responses from noise responses; and 3) their population neural trajectories encoded the target's SNR. Further, we found neurons with significant spectro-temporal tuning properties were less likely to be modulated by task parameters than those neurons that did not have significant tuning properties. Overall, we found that visual stimuli modulated A1 activity and improved the encoding of auditory stimuli by A1 neurons, which might facilitate auditory perception.

Disclosures: H. Cai: None. **Y.E. Cohen:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.02/F31

Topic: D.05. Auditory and Vestibular Systems

Title: Congruent visual information enhances phoneme selectivity in auditory cortex

Authors: *Y. LI, I. DEWITT, D. BRANG;
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Visual speech information, such as lipreading, facilitates spoken word recognition. The neural mechanisms that support audiovisual speech perception remain poorly understood. To address how visual speech affects phoneme processing in auditory areas, we used intracranial EEG (iEEG) signals recorded in epilepsy patients during an audiovisual speech perception task. Participants listened to audio recordings either in isolation or with matching video recordings. Speech stimuli were words composed of 4 initial phonemes (/b/, /g/, /d/, /f/) and balanced following vowels or diphones. To quantify the selectivity of information processing during

speech perception in auditory cortex, high-gamma power was used to calculate a phoneme selectivity index (PSI) for each phoneme and each electrode. For each electrode, we derived a total PSIs across phonemes to represent general sensitivity to phonemes and used the distribution of PSI values across phoneme categories to measure the neural selectivity of phonemes. Preliminary analyses indicate that congruent visual speech improved phoneme selectivity in neuronal populations located in the superior temporal gyrus. Specifically, results showed that audiovisual relative to audio-only trials generated higher total PSI values as well as less uniform distributions across phoneme categories. These data support a model of speech processing in which congruent visual information enhances the acuity of phoneme representations in the auditory system during speech perception.

Disclosures: Y. Li: None. **I. DeWitt:** None. **D. Brang:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.03/F32

Topic: D.05. Auditory and Vestibular Systems

Support: FONDECYT 1220607
ANID BASAL FB0008
Beca Doctorado Nacional ANID 2022-21221090

Title: Dynamics of EEG and Otoacoustic Emissions During Acoustic Residual Inhibition in Tinnitus.

Authors: *S. P. SAN MARTIN[1], C. DE GATICA S.[2], V. MEDEL[3], C. DRAGICEVIC[4], P. H. DELANO[2,5], C. DEVIA[2,6];
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Abstract: Background and Aim:Tinnitus is a phantom sound perception in the absence of stimulation, it affects quality of life and has a prevalence of up to 14% in older adults. Recent studies suggest its cerebral nature, but the neurophysiological mechanisms involved remain uncertain. Our research aims to elucidate cortico- cochlear oscillatory dynamics during tinnitus using the residual inhibition paradigm, which temporarily suppresses tinnitus via broadband noise.Methods:We propose a case-control study recruiting individuals between the ages of 18 and 50 from the Hospital of the University of Chile. All participants will provide their consent through an informed document approved by the hospital's ethics committee. To be included in the study, subjects must have chronic tinnitus (>3 months), unilateral form, and have normal auditory thresholds. Two groups will be established: those who respond to residual inhibition

(cases) and those who do not (controls). The evaluation protocol will consist of recording the audiological profile and functional profile of the tinnitus. Later we'll be subjecting them to a 15-minute electroencephalographic protocol using a residual inhibition paradigm of tinnitus. The main point of comparison between both groups will be spectral powers and synchrony in various frequency bands, both cortical and cochlear, during the EEG protocol.Results:Preliminary results affirm the protocol's feasibility in capturing EEG signals, distortion product otoacoustic emissions (DPOAE), and subjective tinnitus intensity during residual inhibition paradigm. We anticipate that responders will exhibit distinct cortico-cochlear changes, such as heightened EEG alpha band power linked with low-frequency changes in cochlear activity (<10 Hz), especially after prolonged auditory masking. These novel methodology and eventual findings could illuminate tinnitus pathophysiology and guide tailored therapeutic interventions based on residual inhibition of tinnitus.Conclusion:This study seeks to shed light on the complex neurophysiological mechanisms of tinnitus, focusing on the efferent auditory system's role. By employing a multidisciplinary approach and leveraging the residual inhibition paradigm, we aim to provide valuable insights that may pave the way for personalized therapeutic strategies. The integration of cortical and cochlear dynamics represents an innovative approach that could significantly contribute to our understanding of this challenging condition.

Disclosures: S.P. San Martin: None. **C. De Gatica S.:** None. **V. Medel:** None. **C. Dragicevic:** None. **P.H. Delano:** None. **C. Devia:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.04/F33

Topic: D.05. Auditory and Vestibular Systems

Support: William Demant Foundation 22-4035
Faculty Psychology and Neuroscience

Title: Reverberation effects on behavioral and neural speech tracking in two-speaker situations

Authors: A.-L. KRAUSE, ***L. HAUSFELD**;
Cognitive Neurosci., Maastricht Univ., Maastricht, Netherlands

Abstract: In two-talker situations, listeners need to segregate a stream of interest from a second stream. Our auditory system utilizes several cues to support segregation and intelligibility of the relevant speech stream. Most cues were investigated using short and anechoic speech and the effects of reverberation on the underlying neural processing in naturalistic listening situations remain unclear. In this study, we presented participants (N = 18) with two simultaneous speakers while their neural responses were measured with high-density EEG. Using the image method, we computed binaural room impulse responses (BRIRs) to simulate mild and strong reverberation for speakers that were co-located or separated in azimuth. In addition, speech signals were

manipulated to create small or large pitch separation between speakers. The analyses of behavioral responses (intelligibility and difficulty) showed main effects of reverberation and azimuth separation. To investigate cortical responses to reverberant, continuous speech, we employed a linear systems approach using multivariate temporal response functions (mTRFs). In line with behavioral results, decoding of the non-reverberant (‘dry‘) speech in the reverberant mixture showed a strong main effect of reverberation in addition to smaller main effects of location and pitch showing that the auditory system is sensitive to these cues, in particular reverberation, with the current experimental setup. Using speech encoding, we found that non-reverberant speech was more strongly represented compared to reverberant speech signals already at early processing stages (80-100 ms) suggesting early ‘dereverberation’ in the processing hierarchy. In addition, dry speech was more strongly represented in mild vs. strong reverberation conditions at a later stage (> 200 ms) indicating stronger linguistic processing likely due to successful speech extraction and segregation. These results and ongoing analyses help to shed more light on neural processes underlying speech perception in naturalistic, reverberant situations.

Disclosures: A. Krause: None. **L. Hausfeld:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.05/F34

Topic: D.05. Auditory and Vestibular Systems

Support: NIH NIDCD R01 DC020717
University of Michigan LSA UROP

Title: Informative visual input modifies selectivity for speech sounds in superior temporal cortex

Authors: *I. DEWITT[1], Y. LI[1], C. ADAMS[1], E. ZHANG[1], A. MAJUMDAR[1], C. CAO[1], W. C. STACEY[2], D. BRANG[1];
[1]Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Neurol., Univ. of Michigan, Saline, MI

Abstract: Lipreading can augment and facilitate speech perception. The neural mechanisms of multimodal processing in speech perception remain poorly understood. To investigate the hypothesis that informative visual input sharpens speech sound representations in auditory cortex, we recorded intracranial electroencephalography (iEEG) data from patients with intractable epilepsy during naturalistic audiovisual stimulation. Participants viewed a series of short film clips from the Human Connectome Project 7T Protocol that contain instances of speech where a speaker's face may be on screen or not and where other faces may also be on screen. To assess phoneme representations in auditory cortex in the presence of speaker and non-speaker faces, stimuli were annotated for phoneme and face content. Phoneme induced high-gamma band power responses were recorded from contacts in superior temporal cortex,

including Heschl's gyrus. Contacts were initially assessed for change in high-gamma power relative to rest. Stimulus responsive contacts were then assessed for selectivity in phonemic representation, where selectivity was operationalized as the discriminability of phoneme categories from the high-gamma signal. Discriminability was assessed as the mean of the Area Under the Curve for all pairwise phoneme-category Receiver Operating Characteristic curves, which was compared to an approximate-permutation-test null model. Phoneme selectivity was observed in both face conditions. We then tested for change in selectivity as a function of the speaker's face being visible. Consistent with visual speech increasing the precision of neuronal representations in auditory cortex, relative to speech accompanied by a non-speaker face, congruent audiovisual speech was associated with increased selectivity in superior temporal cortex.

Disclosures: I. DeWitt: None. **Y. Li:** None. **C. Adams:** None. **E. Zhang:** None. **A. Majumdar:** None. **C. Cao:** None. **W.C. Stacey:** None. **D. Brang:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.06/F35

Topic: D.05. Auditory and Vestibular Systems

Support: Fondation pour l'Audition (FPA-RD-2021-10)
Agence Nationale de la Recherche (ANR-21-CE37-0002)

Title: Effects of transcranial alternating current stimulation on speech perception can be explained by cutaneous entrainment

Authors: J. ERKENS, R. K. PARI, M. INYUTINA, M. MARX, F. H. KASTEN, *B. ZOEFEL; Ctr. de Recherche Cerveau et Cognition (CerCo), CNRS, Toulouse, France

Abstract: Neural activity aligns to the syllable rhythm of speech, an effect often termed "neural entrainment". This process has become ubiquitous in current theories of speech processing, given that neural entrainment correlates with successful perception of speech. Indeed, studies that used transcranial alternating current stimulation (tACS) to manipulate neural entrainment have demonstrated a causal role of entrainment for speech processing. Nevertheless, the relative contribution of neural entrainment to target and distractors for speech perception in a setting with multiple competing speakers remained unclear. Moreover, it has been shown that transcutaneous stimulation of peripheral nerves can explain some tACS effects, but this confound has never been explored in tACS studies on speech perception. Here, we used tACS to manipulate entrainment to two simultaneously presented sequences of rhythmic speech, whilst participants attended to one of them. A random temporal relationship between speech streams allowed us to disentangle effects of tACS on target- and distractor processing, and to examine their combined effect on a behavioural measure of speech perception. tACS was applied bilaterally to target

entrainment in two regions shown to be instrumental for speech perception (superior temporal gyrus and inferior frontal gyrus). In a control condition, tACS electrodes were placed close to each other to produce similar cutaneous stimulation but a significantly reduced direct brain stimulation. We found that the phase relation between tACS and both target and distracting speech modulated word report accuracy, and to a similar degree. The strength of phasic modulation of target processing correlated with that of the distractor across subjects, and their combined effect on speech perception was stronger than each of the two alone. Importantly, these effects were also observed in the cutaneous control condition. Our findings therefore show (1) that entrainment to target and distracting speech jointly and causally contributes to speech perception, and (2) that tACS entrainment effects on speech perception might not be driven by direct cortical stimulation, but rather follow an indirect somatosensory pathway. These results have major implications for the development of tACS as a stimulation method, as they illustrate the urgent need for cutaneous control conditions, but also suggest somatosensory stimulation as an alternative for a manipulation of speech perception.

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Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.07/F36

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01-DC019394

Title: Continuous and concurrent auditory TRFs using both EEG and MEG reveal processing hierarchies during natural speech of competing speakers

Authors: *K. D. LERUD[1], V. COMMURI[1], C. FISHER[1], S. ANDERSON[1], B. BABADI[1], S. E. KUCHINSKY[2], J. Z. SIMON[1];
[1]Univ. of Maryland, College Park, MD; [2]Walter Reed Natl. Military Med. Ctr., Bethesda, MD

Abstract: Listening to speech in noise is an everyday occurrence made possible, if conditions allow, by complex neural processes. Specifically, listening to one person's voice in the midst of one or more competing voices is often called the cocktail party problem, and is a task that lends itself to experimental investigation because of its naturalistic nature and the ease of parametric control. Here, we record simultaneous EEG and MEG, as well as multiple behavioral measures, from normal hearing younger adults as they attend to one of two competing speakers, at several different signal-to-noise ratios (SNRs), reading a narrative text.
Using the temporal response function (TRF) paradigm with respect to the EEG and MEG responses, we analyze auditory responses from both the brainstem and cortex. Stimulus regressors are constructed to represent a hierarchy of auditory and language-based features from

both the target and distractor speakers, from which multiple TRFs are calculated. These TRFs are also analyzed to determine which aspects of auditory brain responses are modulated by selective attention, and to what extent. EEG, which is sensitive to deep auditory sources, allows estimation of faster time-scale TRFs, calculated with regressors corresponding to a cochlea and auditory nerve model. MEG allows estimation of slower time-scale TRFs, calculated with slower regressors corresponding to features of the speech signal such as the envelope and envelope onsets, as well as linguistic features at the phoneme and word level.
A hierarchy of speech-related TRFs and their corresponding sources is thus measured concurrently, including at the latencies of the auditory brainstem response (ABR, 0 - 15 ms), middle latency response (MLR, 15 - 60 ms), N1-P2 complex (60 - 200 ms), and slower linguistic responses (120 - 800 ms).
We find little evidence that faster TRFs from early auditory areas depend on the speaker identity regressor (target vs. distractor), but can demonstrate that later auditory and linguistic cortical TRFs exhibit a wide range of levels of the effect of selective attention. Some results in the recent literature are mixed with regard to attentional modulation of ABR- or frequency following response (FFR)-type responses; this novel approach that combines concurrent source-space EEG and MEG and separate families of TRF regressors for each speaker, may help to shed further light not only on how the cortex differentially tracks an attended speaker, but also on how the earlier auditory system may or may not do the same.

Disclosures: K.D. Lerud: None. **V. Commuri:** None. **C. Fisher:** None. **S. Anderson:** None. **B. Babadi:** None. **S.E. Kuchinsky:** None. **J.Z. Simon:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.08/F37

Topic: D.05. Auditory and Vestibular Systems

Support: FWO 12AF124N

Title: High-resolution fmri reveals a large cortical network responding to conspecific emotional vocalization in macaques

Authors: *M. FROESEL[1,2], Q. ZHU[3], K. IKUCHI[4], H. WANG[5], S. BEN HAMED[6], W. VANDUFFEL[7,8];
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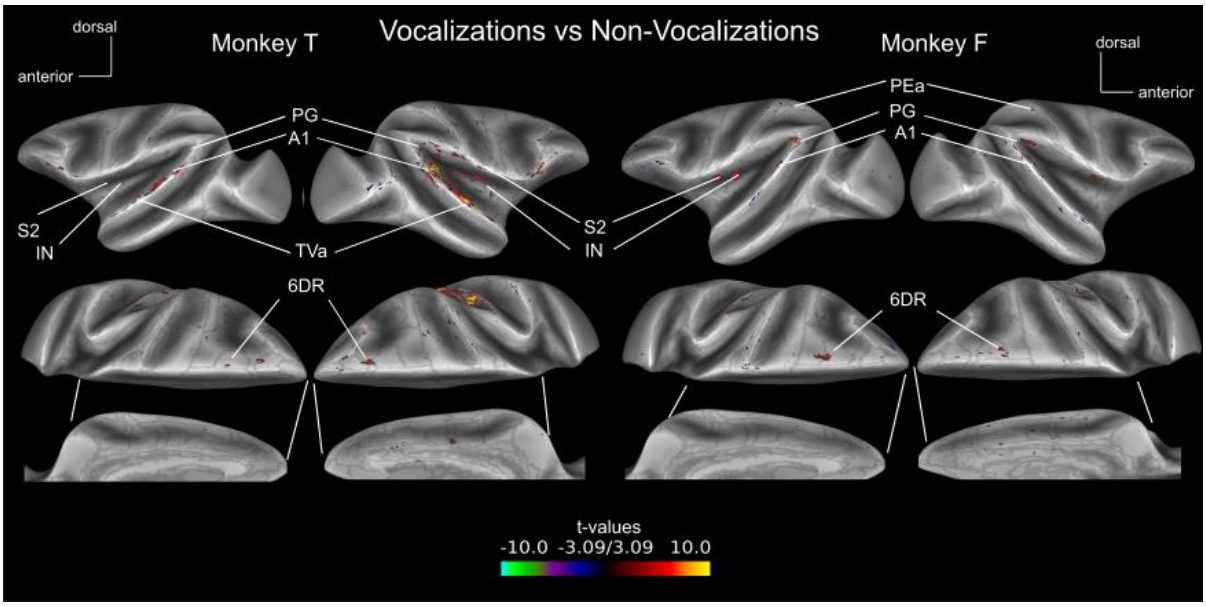
Abstract: Understanding the neural basis of social communication and emotional processing in human and non-human primates is one of the current challenges in systems neuroscience. Studies using neuroimaging techniques such as fMRI and electrophysiological recordings have identified several cortical areas in primates as being voice sensitive, a.k.a. voice patches. These voice patches are considered crucial for processing and distinguishing various vocalizations made by individuals of the same species (see Belin et al., 2018; and Bondin et al., 2021). In this study, we used fMRI (0.6 isotropic voxels) to investigate brain areas dedicated to conspecific vocalization processing in two awake *rhesus monkeys*. While these macaques were fixating a central cross on a screen, they were exposed to several types of vocalization with different emotional and semantic content. Specifically, we presented coos, screams and aggressive calls; in addition to other animal calls, nature sounds and a scrambled version of each stimulus category. Using a combination of parametric and non-parametric analyses, we identified several voice-sensitive cortical areas in single subjects and both hemispheres. Some of these voice patches were not yet described in the literature. In all 4 hemispheres, we obtained voice-sensitive activations located in the dorsal premotor cortex and in the most caudal part of the lateral sulcus. Moreover, fMRI responses in some of the latter cortical areas were distinctively activated by specific monkey calls. In conclusion, our sub-mm resolution functional imaging data suggest that the voice-processing network in rhesus monkeys is more elaborated than previously thought.



Disclosures: M. Froesel: None. **Q. Zhu:** None. **K. Ikuchi:** None. **H. Wang:** None. **S. Ben Hamed:** None. **W. Vanduffel:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.09/Web Only

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC019278

Title: Neural encoding of spectral structures in marmoset vocalizations

Authors: D. NGUYEN, ***Y. ZHOU**;
Arizona State Univ., Tempe, AZ

Abstract: Animal vocalizations are critical communication signals for a species to engage in social interactions such as mating selection, predator warning, and territorial control. Marmoset calls typically exhibit harmonic spectral structures covering the frequency range of 5-40 kHz, and contain dynamic envelope modulation and repetitive temporal structures (e.g., twitters). In the primary auditory cortex (A1) of marmosets, neurons respond in a phase-locked manner to envelope features of sounds, akin to time-division multiplexing (Zhou and Wang, 2010). In this study, we investigated whether time-division multiplexing extends to encoding the harmonic spectral structures observed in marmoset calls. We collected single-unit responses from the A1 of two marmoset monkeys using high-density silicon probes to sample neural activities simultaneously across cortical layers. We investigated how temporal response features (onset, offset, sustained, and their combinations) manifest in the time-multiplexing space between using intact vocalizations and their spectral variations with identical envelope modulation. Our findings showed that temporal response signatures, as defined, are not static properties of A1 neurons. Spectral variations induce shifts between the onset, offset, and sustained patterns, thereby altering the temporal sequence of unit responses within the neuronal population. These results suggest that instead of recruiting distinct neurons for different stimuli (place code), the same group of A1 neurons may encode varied stimuli by modifying their temporal response orders. This form of time-division multiplexing code, which has been observed in other animal species, likely plays an important role in auditory pattern recognition.

Disclosures: D. Nguyen: None. **Y. Zhou:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.10/G1

Topic: D.05. Auditory and Vestibular Systems

Title: Global and laminar representation of vocalizations in marmoset brain

Authors: ***D. CHEN**, K. ZHANG, M. PEI, Y. LUO, B. WANG, Z. LIANG;
Inst. of Neuroscience, CAS, Shanghai, China

Abstract: Conspecific vocalizations (CVs) constitute a fundamental aspect of human language. However, a comprehensive understanding of vocalization perception in the marmoset brain

remains elusive. Our study utilized awake marmoset auditory functional magnetic resonance imaging (fMRI) with blood oxygenation level-dependent (BOLD) contrast for whole brain activation mapping and cerebral blood volume (CBV) contrast for laminar profiles of auditory related brain regions at a 9.4T scanner. Four types of CVs from two adult male marmosets (aged 2-5 years) and their phase-scrambled counterparts were presented in a block design during fMRI scanning. Four adult male marmosets (aged 2-5 years) participated in BOLD study. Five adult male marmosets (aged 2-5 years) participated in CBV study, two of which also participated in the BOLD experiment. For BOLD study, group level one-sample t-tests revealed significant activation induced by both intact and phase-scrambled marmoset vocalizations in the inferior colliculus (IC), medial geniculate nucleus (MGN), AuC, visual cortex (VC), parainsular cortex (Pal), and prefrontal cortex (PFC). Moreover, significant differences between the two sound types were found in IC, AuC, and PFC regions. Subsequently, a group analysis employing within-subject three-way ANOVA (scramble×caller identity×call-type) showed significant main effects of call-type and scramble in the AuC. Notably, caller identity did not yield a significant main effect. Furthermore, a significant interaction effect between call type and scramble was detected in the AuC, confirming the differences between intact and phase-scrambled vocalizations across different types. Further multivariate pattern analysis (MVPA) revealed that population neural activity pattern in amygdala, insular cortex (Ins) and Pal, secondary somatosensory area a (S2a), and area 31 (A31) in posterior cingulate and restrospenial regions (PCRSC) could decode information of call type or scramble. In CBV study, we found peak activations induced by all sounds in the AuC and adjacent Pal localized at the middle layers of the cortex. In conclusion, our study offers insights into the neural processing of vocalizations in various marmoset brain regions, therefore advancing our understanding of the neural underpinnings of social communication.

Disclosures: D. Chen: None. **K. Zhang:** None. **M. Pei:** None. **Y. Luo:** None. **B. Wang:** None. **Z. Liang:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.11/Web Only

Topic: D.05. Auditory and Vestibular Systems

Support: R01DC014950
R21DC021048

Title: Representation of space in auditory cortex of freely moving animals

Authors: *J. WINGERT[1], B. BURAN[2], S. V. DAVID[2];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]OHRC, Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Auditory encoding is traditionally studied in head-fixed preparations, largely out of necessity to control acoustic conditions. This constraint has created a gap in knowledge about auditory processing in complex naturalistic conditions in which a listener can dynamically change their position with respect to sound sources. Recent work in both auditory cortex and other sensory modalities has shown that cortical neurons can encode a broad range of non-sensory information, including location and task-related variables. Studies of non-sensory encoding typically do not consider the impact of these variables on the concurrent sensory representation. To overcome this gap, we performed large scale semi-chronic Neuropixel recordings in ferret auditory cortex while animals freely navigated a behavioral arena during a go/no-go tone detection behavior. During the task, a continuous background of natural sounds was played, which maximized the diversity of natural stimuli presented to the animal. Simultaneous tracking of head position and angle permitted virtual head fixation by modeling stimuli reaching the ear following transformation by the head-related transfer function. This framework allowed for robust characterization of auditory responses while animals behaved freely. Decoding from populations of auditory neurons revealed representation of non-auditory variables, including position, velocity, and head direction, consistent with findings from other groups using rodent models. Also, a multimodal auditory and spatial-motor encoding model predicted single neuron activity better than models including only auditory related activity. Surprisingly, most of the improvement in prediction accuracy could be accounted for by a gain/offset model in which spatial-motor variables were used to modulate gain and offset of predictions by an auditory-only model. The output of the spatial-motor gain/offset auditory model, along with positional decoding and simple 2D-tuning curve representations of neural activity suggest that position within the behavioral arena is the dominant component impacting auditory responses. This observation contrasts with studies of movement-related activity in auditory cortex in head-fixed rodent preparations in which animals can move on treadmills/spheres, which find suppression during motor activity. Together, these findings demonstrate that representation of position is tightly interwoven with representation of relatively low-level sound features in auditory cortex. How this multimodal code is utilized by downstream perception and behavioral processes remains an open question for future study.

Disclosures: J. Wingert: None. **B. Buran:** None. **S.V. David:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.12/G2

Topic: D.05. Auditory and Vestibular Systems

Title: Neural Discrimination of Vocalization in the Auditory Cortex of the Mexican Free-tailed Bat

Authors: *V. HERNANDEZ-CASTANON[1], S. MACIAS[2];
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Abstract: We investigated the neural basis of auditory processing for communication calls in the Mexican free-tailed bat, Tadarida brasiliensis, a species known for its complex and highly elaborate vocal repertoire. We addressed the question of whether the encoding of conspecific call types depends on the response selectivity of individual neurons or the collective response of multiple neurons within a structured layer organization in the primary auditory cortex. We analyzed the selectivity and decoding properties and layer organization for neurons in response to ten types of communication calls and two types of sonar pulses as acoustic stimuli. We found that neurons in the primary auditory cortex exhibit a wide range of selectivity to these social calls, indicating a diverse neural tuning. Moreover, we identified collective processing mechanisms in the auditory neurons for decoding call types. This was achieved using supervised classification based on the neuron's firing rate relative to the baseline activity (measured as the Z score) and temporal components defined by the interspike intervals (ISI) of the neuron's action potentials. This approach provided an understanding of how auditory neurons process and differentiate between different call types, emphasizing the importance of both the rate and timing of neuronal firing in the auditory decoding process. This mechanism indicates that the distinction among communication calls relies on a neural ensemble capable of modulating their response to a spectrum of sound features across different cortical layers. Our findings contribute to a deeper understanding of the neural mechanisms underlying auditory processing in the Tadarida brasiliensis bat model, highlighting the complexity of neural encoding in bat communication.

Disclosures: V. Hernandez-Castanon: None. **S. Macias:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.13/G3

Topic: D.05. Auditory and Vestibular Systems

Support: NIH R15 DC020327-01

Title: Localization of dopamine D2a and D1Aa receptor expression in the central auditory system of a vocal fish

Authors: *K. KOBI, P. M. FORLANO;
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Abstract: The plainfin midshipman is a seasonally reproducing, vocalizing fish with robust increases in peripheral auditory sensitivity during the summer breeding season that enhance the detection of social acoustic signals for reproduction. In the summer, robust decreases in dopamine innervation of the inner ear coupled with decreased expression of the inhibitory dopamine D2a receptor contribute, in part, to their enhanced auditory sensitivity. Seasonal changes in catecholaminergic innervation of central auditory nuclei are also observed, however, the functional role of dopamine in these areas is less clear, particularly its role in modulating

auditory sensitivity and auditory processing. As a first step towards elucidating the function of dopaminergic action on the central auditory system, we utilized fluorescence in situ hybridization (HCR RNA-FISH) to characterize the expression of inhibitory dopamine D2a and excitatory dopamine D1Aa receptor transcripts in the brains of adult female midshipman fish in reproductive condition. Our preliminary data suggests both D1Aa and D2a receptor expression in telencephalic (medial area dorsalis of the telencephalon, supracomissural nucleus), diencephalic (anterior tuberal nucleus, central posterior nucleus of the thalamus), midbrain (torus semicircularis), and hindbrain (descending octaval nucleus) auditory nuclei. Robust D2a but not D1Aa expression appears to be localized to the dopaminergic neurons in the periventricular posterior tuberculum, which are responsible for driving the seasonal changes in dopamine innervation of the inner ear and also innervate other central auditory centers. Lastly, D2a receptor expression seems to generally predominate over D1Aa receptor expression throughout the brain. These findings provide a first step towards understanding the modulatory role of dopamine in the central auditory system and a foundation for future seasonal and sex comparisons in a vocal vertebrate.

Disclosures: K. Kobi: None. **P.M. Forlano:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.14/G4

Topic: D.05. Auditory and Vestibular Systems

Support: BrainPlay-ERC-Synergy grant

Title: Neuronal recordings and pharmacolocial interventions suggest rat auditory cortex controls vocal production and the effects of noise on vocalizations

Authors: *W. TANG, **M. A. CONCHA**, M. BRECHT;
Bernstein Ctr. for Computat. Neurosci. Berlin, Berlin, Germany

Abstract: Vocal communication is believed to play a pivotal role in regulating social interactions across many animal species. Continuous assessment of vocal feedback is essential for precise sound emission during communication. The most ubiquitous signalling strategy recruiting the vocal-feedback mechanisms is recognized as the Lombard effect. The Lombard effect, together with spectro-temporal modifications of vocalizations, is called noise-induced vocal modifications (NIVMs). However, in spite of the functional importance of NIVMs, there is very limited study investigating the role of brain areas or circuits in this vocal feedback-dependent behaviour. We here performed the first detailed study in which rats show robust compensatory increases in mean call frequency and relatively weak but significant increases in mean call intensity, as well as decreased total call duration during white noise. Furthermore, during rat vocalization, some auditory cortex neurons exhibited pre-call activity or different

patterns of responses during call and playback. Classification of auditory cortex neurons according to these features revealed five distinct functional cell types: Pre-call, Onset Activated, Onset Inhibited, Ramping Activated and Ramping Inhibited neurons. All these cell types showed significant differences when comparing their activity during call and playback. Some of these cells also showed a specific cortical depth profile. Among these types of neurons, Onset Inhibited cells located in the lower layers of the cortex, predict vocal duration and call occurrence. At the same time, these cells showed limited neural activity during white noise stimulation in the 100 ms time window before call onset, making them a strong candidate underlying the observed behavioural changes in vocalizations. Additionally, by injecting muscimol (a GABA A receptor agonist) or gabazine (a GABA A receptor antagonist) into the auditory cortex bilaterally, we show that rat vocal emissions can be modulated bidirectionally. Importantly, suppressing auditory cortex neuronal activity in the presence of white noise can partially mitigate the impact of noise-induced vocal modifications. In the end, our anterograde and retrograde tracing experiments yield further elucidation regarding the possible output pathways arising from the auditory cortex, which might play a role in mediating the effects of noise-induced vocal modifications in rats.

Disclosures: W. Tang: None. **M.A. Concha:** None. **M. Brecht:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

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Program #/Poster #: PSTR460.15/G5

Topic: D.05. Auditory and Vestibular Systems

Support: R01DC018353 (NIDCD)
Nancy Lurie Marks Family Foundation
5R01DC000937-30

Title: Subpopulations of excitatory and inhibitory neurons in auditory cortex show selective responses to salient vocalizations

Authors: *Z. GHASEMAHMAD[1], E. CHIN[2], M. THOMAS[3], C. G. SWEENEY[3], J. J. WENSTRUP[4], A. E. TAKESIAN[5];
[1]Mass. Eye and Ear; Harvard Med. Sch., Boston, MA; [2]Massachusetts Eye and Ear; Harvard Col., Cambridge, MA; [3]Massachusetts Eye and Ear; Harvard Med. Sch., Boston, MA; [4]Dept. of Anat. and Neurobio., Northeast Ohio Med. Univ., Rootstown, OH; [5]Otolaryngology, Massachusetts Eye and Ear; Harvard Med. Sch., Boston, MA

Abstract: Mice emit a repertoire of complex vocalizations during different behavioral contexts, including courtship and aggressive interactions. Playback of these vocalizations can elicit distinct behavioral responses and neuromodulatory release patterns in the brains of listening mice that depend upon behavioral state and experience. Auditory cortex is thought to provide information

about the identity of the vocalization to the motor and emotion centers of the brain involved in shaping these behavioral reactions. However, the representation of these salient vocalizations within neuronal subpopulations across auditory cortical regions is not well understood. To address this, we focused on pyramidal excitatory neurons and a subpopulation of inhibitory interneurons expressing Neuron-Derived Neurotrophic Factor (NDNF) which are believed to shape cortical responses in a state-dependent manner. Using transgenic mouse lines that express genetically-encoded calcium indicators (GCaMP) in either cortical pyramidal neurons or NDNF interneurons, we performed widefield and two-photon calcium imaging from the auditory cortical regions in awake head-fixed mice. Playback of distinct vocalizations induced robust activity across the primary auditory cortex (A1), anterior auditory field (AAF), and multiple higher-order auditory cortical fields. Furthermore, subsets of L2/3 and L4 pyramidal neurons and NDNF interneurons show strong selectivity to specific vocalizations or vocalization classes (mating versus stress calls). Many of these neurons show robust responses to these vocalizations, but not to sound stimuli with the same spectral content. A small number of vocalization-selective cortical neurons can accurately decode the vocalization identity. Our ongoing experiments are examining the behavioral state- and experience-dependent responses to these vocal stimuli within specific auditory cortical regions. Together, these studies will provide insight into the processing of salient vocalizations within specific circuits across auditory cortical fields.

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Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

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Program #/Poster #: PSTR460.16/G6

Topic: D.05. Auditory and Vestibular Systems

Support: F32 DC018721-01A1
R01DC013826-07
R01MH117778-05

Title: Effects of acute and chronic auditory feedback distortion on mouse vocalization

Authors: *T. HARMON[1], R. D. MOONEY[2];
[1]Duke Univ., Durham, NC; [2]Med. Ctr., Durham, NC

Abstract: Vocalization generates auditory feedback which allows the brain to detect vocal-motor errors and modify subsequent performance. In both humans and marmosets, systematic distortions of auditory feedback lead to adapted vocal performance, a capability that is likely supported by the auditory cortex. An influential idea is that auditory cortical neurons receive vocal-motor corollary discharge signals that suppress responses to expected features of vocal feedback. To further elucidate the neural mechanisms that support feedback-dependent vocal

control, we tested whether mice adapt their vocal performance to compensate for distorted auditory feedback induced by exposure to helium-enriched (heliox) air. We compared the frequency of USVs produced in a range of helium concentrations to heliox USVs produced by TMC1-/- congenitally deaf mice. We found that the frequencies of USVs produced by hearing mice were slightly lower than USVs produced by deaf mice, consistent with feedback-dependent compensation. In addition, the frequency of USVs produced by hearing mice in a heliox environment across multiple days was highly stable, indicating that while mice modestly adapt their vocal performance in response to acute heliox exposure, they do not adapt further across extensive auditory feedback distortion. To test how auditory cortical neurons monitor vocal performance, we conducted two photon imaging of pyramidal neurons and interneurons in the auditory cortex of a head-fixed male mouse during vocalization to a female mouse, or while playing back USVs. This approach revealed a large corpus of auditory cortical neurons that were modulated by vocalization. Vocal modulation often preceded the onset of vocalization and was detected in both deaf as well as hearing mice, indicating the influence of a vocalization-specific motor signal. Additionally, most neurons showed a mix of activation, suppression, or no response across vocal bouts with different acoustic properties, consistent with the variable integration of suppressive vocal motor signals and activating auditory feedback signals. In on-going experiments, we are testing how this population of vocalization-modulated auditory cortical neurons respond when vocal feedback is distorted by heliox air.

Disclosures: T. Harmon: None. **R.D. Mooney:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.17/G7

Topic: D.05. Auditory and Vestibular Systems

Support: K99DC021581
F32MH123016
U19NS107616

Title: Projection-specific cortical processing of vocalizations driving mouse maternal behavior.

Authors: *A. M. LEMESSURIER[1], A. AGHA[2], G. KAUR[3], J. STEPHENS[1], R. C. FROEMKE[4];
[1]Neurosci. Inst., NYU Sch. of Med., New York, NY; [2]Neurosci. Inst., New York Univ., New York, NY; [3]Neurosci. Inst., NYU Langone, New York, NY; [4]Otolaryngology, NYU Med., New York, NY

Abstract: How does the brain derive meaning from social vocalizations and drive behavior in response? Vocalizations are complex stimuli that must require integration across multiple time-scales and appropriate contextualization. Thus it is likely that top-down modulation of feed-

forward auditory processing is needed for these computations. To test this hypothesis, we took advantage of a robust mouse behavior, in which parental animals search for lost pups in response to infant ultrasonic vocalizations (USVs). Experienced moms are experts at this behavior, but nulliparous females can also learn to respond to infant distress calls after cohousing with lactating moms and litters, and emergence of pup retrieval behavior is correlated with oxytocin-dependent plasticity in the left auditory cortex (Marlin et al. 2015, Schiavo et al. 2020). We first asked whether projections from auditory cortex to subcortical areas are important for pup retrieval behavior in experienced maternal mice by chemogenetically silencing activity in left auditory cortex layer 5 during retrieval. Pup retrieval was reduced after CNO treatment vs vehicle control sessions (N=6 mice, $p<0.05$). Silencing only neurons projecting to inferior colliculus led to a similar decrease (N=6, $p<0.05$), while silencing only neurons projecting to the tail of striatum had no effect (N=6, $p>0.05$), indicating that corticocollicular (CC) projections are particularly critical for linking perception to behavior. We next used 2-photon Ca^{2+} imaging in awake head-fixed mice to compare USV responses of corticostriatal (CS) and CC neurons. CC neurons in expert retrievers (N=4 mice) had sustained increases in activity during USVs compared to pure tones, while activity was similar during USV and tone presentation in CS neurons (N=3 mice). To precisely quantify the time course of these USV responses, we performed in vivo whole-cell recordings from optotagged projection neurons (n=8 CC, n=5 CS neurons). We also performed simultaneous Neuropixels recordings from auditory cortex, midbrain, and thalamus (N=6 mice) and found a subpopulation of neurons that did not respond to single call syllables but instead integrated over longer USV sequences. To examine whether sustained activity in corticofugal neurons develops with experience, we tracked activity in CC and CS neurons with 2-photon imaging over days of co-housing. This revealed robust responses to USVs on each day; however, responses were variable across individual neurons and days. In both groups, delayed and sustained responses to USVs were larger on days in which mice had reached expert performance, which may reflect upregulated activity in recurrent auditory circuits.

Disclosures: A.M. Lemessurier: None. **A. Agha:** None. **G. Kaur:** None. **J. Stephens:** None. **R.C. Froemke:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

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Program #/Poster #: PSTR460.18/G8

Topic: D.05. Auditory and Vestibular Systems

Support: NIH R01DC018621

Title: Intrinsic Plasticity in the Developing Zebra Finch Auditory Cortex Depends on the Timing and Acoustical Statistics of Experience.

Authors: *B. BELLANGER, Y. LU, C. MELIZA;
Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The zebra finch (*Taeniopygia guttata*) is a social songbird that communicates through innate and learned vocalizations, and early auditory experience is crucial for development of auditory processing. We showed in previous studies that the intrinsic dynamics of neurons in the caudal mesopallium (CM), a higher-order auditory area, depend on whether birds are raised in a naturalistic, complex social-acoustical environment. Specifically, birds that are raised without exposure to the "cocktail-party" background of a zebra finch colony have reduced expression of Kv1.1, a low-threshold potassium channel, and fail to develop the phasic-spiking dynamics that characterize about half of the neurons in typically raised birds. Based on these results, we hypothesize that intrinsic plasticity is an adaptative mechanism that permits normal developmental learning when the auditory cortex is bombarded by the songs and calls of many individuals. To test this hypothesis, birds were raised in acoustic isolation chambers in which we continuously played a recording of the colony or noise that was matched to one or more acoustical statistics of the colony recording. This allowed us to separately test the contributions of non-vocal social interactions and of specific acoustical features to the development of phasic spiking, which we measured using whole-cell recordings in slices. We also systematically varied the timing of noise exposure to test for a critical or sensitive period for this experience-dependent plasticity. Our results show that social interaction with the colony was not necessary for the development of phasic spiking and that broadcasting white noise with amplitude matched to the envelope of colony noise resulted in only a partial rescue of phasic dynamics. This supports our hypothesis that phasic spiking in the cortex is an adaptation to a complex acoustical background that matches the higher-order spectrotemporal structure of song.

Disclosures: B. Bellanger: None. **Y. Lu:** None. **C. Meliza:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.19/G9

Topic: D.05. Auditory and Vestibular Systems

Support: NSERC

Title: The role of serotonin in the estradiol-dependent selectivity of auditory regions in songbirds

Authors: *A. R. S. FLYNN[1], C. J. HENRY[1], G. CASBOURN[2], S. RAMSAY[3], S. A. MACDOUGALL-SHACKLETON[4];
[1]Neurosci., Univ. of Western Ontario, London, ON, Canada; [2]Univ. of Western Ontario, London, ON, Canada; [3]Wilfrid Laurier Univ., Waterloo, ON, Canada; [4]Psychology, Univ. of Western Ontario, London, ON, Canada

Abstract: Behavioural relevance and perception of sociosexual signals are altered by an individual's endocrine state. One of the most notable changes in sensory integration and processing of environmental cues are birdsongs in avian courtship. Breeding-typical levels of estradiol (E2) have been shown to alter selective auditory attention and increase available serotonin (5-HT) in songbirds. This prompts the question if selective auditory attention is induced by E2, or instead influenced by the indirect associated release of 5-HT. Forty-eight female non-breeding white throated sparrows (*Zonotrichia albicollis*) were treated with blank silastic implants, 17β-estradiol, blank implants and fluoxetine, or 17β-estradiol implants and risperidone. Half (n = 24) heard thirty minutes of male conspecific song, and the others were exposed to control tones. We used immunohistochemistry to quantify the immediate early gene ZENK immunoreactivity (ZENK-ir) in auditory regions: caudomedial nidopallium (NCM), caudomedial mesopallium (CMM), and mesencephalicus lateralis, pars dorsalis (MLd). Breeding-typical levels of E2 did not induce auditory selectivity in the NCM, CMM, or MLd. However, there was a significant interaction between drug treatment and sound stimulus in the group treated with the serotonin enhancer (fluoxetine) in the absence of E2 in the CMM, along with non-significant trends occurring in the NCM in the same group. These interactions were not found in MLd. Taken together, these findings suggest 5-HT may be acting as a mediator in the previously observed relationship between E2 and auditory selectivity in higher auditory brain regions.

Disclosures: A.R.S. Flynn: None. **C.J. Henry:** None. **G. Casbourn:** None. **S. Ramsay:** None. **S.A. MacDougall-Shackleton:** None.

Poster

PSTR460: Auditory Processing: Vocalizations and Natural Sounds

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR460.20/G10

Topic: D.05. Auditory and Vestibular Systems

Title: Rapid effects of novel song exposure and 17B-estradiol on dendritic spine density in songbird caudal nidopallium neurons

Authors: *M. FERNANDEZ-VARGAS, R. FLEMING, A. MATSUI, K. LUELL, C. MOELLER, J. LEWIS;
Psychology/Neuroscience, Colorado Col., Colorado Springs, CO

Abstract: The avian caudal nidopallium is a telencephalic region involved in complex cognitive and sensory processing. Moreover, it expresses a diverse array of neurotransmitters and hormones. The caudomedial nidopallium (NCM) has been established as a secondary auditory region involved in auditory learning, memory, recognition, and experience-dependent plasticity. The caudolateral nidopallium (NCL) has been associated with executive control, working memory, learning, reward evaluation and motor planning. It is often referred as the avian analogue of the prefrontal cortex. In songbirds, synaptic plasticity, measured by the formation of

dendritic spines, has been quantified in response to the exposure of conspecific songs early during development and later in adulthood in the NCM. The dorsal NCL is responsive to conspecific song and involved in vocal learning, but synaptic plasticity in response to song has not been studied in this region. In addition, exposure to conspecific song stimulates the synthesis of neuroestrogens in the NCM and both regions express aromatase, the estrogen-synthesizing enzyme. Therefore, this study examined whether the exposure to novel songs can rapidly stimulate the formation of dendritic spines in caudal nidopallium neurons and whether this process can be facilitated by 17B-estradiol (E2) in zebra finches. We exposed individual adult males to 30 m of novel songs playback or silence and the oral administration of E2 (1mg/kg) or vehicle, approximately 1.5 h before brain extraction. The administration route and dose have been previously shown to increase E2 plasma levels within 10 m. The brain tissue was then processed using a Rapid Golgi Stain protocol and stacked imaged at 100x for 3D neuron reconstruction and tracing. A Sholl analysis was performed using Neurolucida software. We found a main effect of novel song exposure on average spine density along the length of dendrites of NCL neurons. The main effect of song was significant also at 100 um from the soma. In NCM neurons, song exposure showed a tendency to stimulate the formation of dendritic spines along the dendrite. At distal parts of the dendrite (110 um), we found a significant interaction between song exposure and E2 suggesting that exogenous E2 stimulated the formation of spines in neurons exposed to novel songs and not to silence. This research reveals for the first time that the NCL region exhibits song-evoked synaptic plasticity in songbirds and has a potential role in adult auditory learning and memory. Moreover, exogenous estradiol may facilitate the formation of dendritic spines at distal locations of the dendrite during novel song stimulation in the NCM.

Disclosures: M. Fernandez-Vargas: None. **R. Fleming:** None. **A. Matsui:** None. **K. Luell:** None. **C. Moeller:** None. **J. Lewis:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.01/G11

Topic: D.06. Vision

Support: Supported by the Human Brain Project (SGA2).

Title: Dendritic synaptome of calcium-binding protein containing GABAergic interneurons in the mouse primary visual cortex

Authors: P. TALAPKA[1], Z. KOCSIS[2], V. SZARVAS[2], ***Z. KISVARDAY**[3];
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Abstract: Complete morphometric characterization of synaptic inputs of GABAergic interneurons (INs) is a key component in exploring their regulatory roles to make predictions in cortical function. For resolving the different structural components of synapses established on the surface of neurochemically distinct IN subtypes, high resolution serial section transmission electron microscopy is an adequate tool. Here we provide a synaptic input database for dendrites of calcium binding protein containing (CBP) INs such as parvalbumin (PV), calretinin (CR), calbindin-D_{28K} (CB). Nine dendrites and all presynaptic boutons (n=830) terminating on their surface were traced and reconstructed in three-dimensions supplemented with postembedding GABA-gold immunolabelling. The following basic parameters of the reconstructed synapses were determined: relative ratio of symmetric (ss) and asymmetric (as) synapses; number of synapses per unit length of dendrites; surface area and volume of presynaptic boutons; area of the active zones of synapses; frequency distribution of synapse types (ss and as per unit length) along the dendrites. Significant differences in the morphometric parameters of excitatory, but not inhibitory inputs were detected between the three subtypes of INs. Surface extent and the number of synaptic inputs on PV dendrites were multifold compared to the other two subtypes (CR, CB). Interestingly, no difference in the basic parameters of presynaptic excitatory and inhibitory boutons were found between IN subtypes. Clustering of the boutons could be observed only for PV dendrites. Applying the above findings on 3D reconstructions of available databases a conservative estimate could be made on the total number of synapses impinging on the dendrites of individual CBP neurons. Our findings provide essential structural information in terms of number and distribution of input synapses to establishing realistic computational models for studying the function of IN subtypes.

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Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.02/G12

Topic: D.06. Vision

Title: Long- and short-duration optogenetic inhibition in the mouse primary visual cortex exerts distinct effects during the luminance discrimination task.

Authors: *S. NISHIMOTO[1,3], M. WATANABE[2], A. FUNAMIZU[3,1];
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Abstract: Various methods, including chemogenetics, optogenetics, and sonogenetics, are utilized in neuroscience to modulate neural activity. Optogenetics, renowned for its precise temporal and spatial control, plays a pivotal role in elucidating neural circuitry by enabling targeted activation and inhibition of specific neural populations. Nevertheless, the specific effects of optogenetic modulation on perception remain elusive. In this study, we investigated the

impact of optogenetic inhibition using CamKIIa-stGtACR2 in the primary visual cortex (V1) during a luminance discrimination task.The task was a Go/No-Go task, simultaneously presenting visual stimuli (0, 12, 255 relative luminance) on left and right screens for 50 milliseconds. If the left stimulus had higher luminance, mice received a water reward by licking a spout (Go trial); otherwise, they had to refrain from licking (No-Go trial). We trained 7 mice for a month and found that the mice achieved an average accuracy of 93.6% and 96.7% during Go trials for 0 vs. 12 and 12 vs. 255 conditions, respectively. On the other hand, No-Go trials had an accuracy of 92.9% and 62.3% for 0 vs. 12 and 12 vs. 255, respectively. Subsequently, we investigated the effects of optogenetic inhibition in V1 during the task. Using intrinsic signal optical imaging, we identified the right V1 region corresponding to the left visual stimulus in each mouse. We then injected pAAV-CamKIIa-stGtACR2-FusionRed and inserted a 200 µm diameter optic fiber into the identified V1 region to optogenetically suppress neural activity in the right visual cortex during the 0 vs. 12 condition. A black rubber cone was placed above the head bar to prevent light leakage. During all trials, there was a 40% probability of delivering blue light (470 nm, 10-15 mW) through the optic fiber. We established two suppression conditions: long-duration suppression, involving neural activity inhibition starting before the presentation of the visual stimulus until after the behavioral response, and short-duration suppression, entailing inhibition for 0.2 seconds following the stimulus presentation. As a result of the inhibition experiment, long-duration suppression reduced accuracy in Go trials ($p = 7.4e-4$, Wilcoxon signed rank test, 6 mice) with no significant changes in No-Go trials ($p = 0.65$). Conversely, under short-duration suppression, mice exhibited high Go rates in both Go and No-Go trials (72.9% and 65.1%, 2 mice, 1163 trials). These findings suggest distinct effects of long- and short-duration suppression during luminance discrimination, despite both conditions suppressing V1 neural activity from stimulus presentation until signal arrival at V1.

Disclosures: S. Nishimoto: None. **M. Watanabe:** None. **A. Funamizu:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.03/G13

Topic: D.06. Vision

Support: R01 HD055453 (NIH-NICHD)
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R01 NS117597 (NIH- NINDS)

Title: Atypical contextual modulation and size tuning in visual cortex of Fragile X mice

Authors: *I. A. TELLO-GARCIA[1], J. HSU[1], C. PORTERA-CAILLIAU[2,1];
[1]Dept. of Neurol., [2]Dept. of Neurobio., UCLA, Los Angeles, CA

Abstract: Atypical sensory processing is a hallmark of Fragile X syndrome (FXS). Sensory hypersensitivity, and how it contributes to gaze aversion, anxiety, attention deficit, and learning delay, has been studied extensively. Differences in visual integration in FXS, which are also prominent in autism, are less understood. Still, they could explain why affected individuals tend to pay greater attention to details in visual scenes but find integrating the whole picture more challenging. This difficulty in seeing 'the forest for the trees' points to differences in how visual information is integrated within the greater context. We previously reported that *Fmr1* knockout (KO) mice and humans with FXS show similar difficulties in visual discrimination. In the mice, these deficits correlated with a decrease in the orientation tuning of pyramidal (Pyr) neurons in the primary visual cortex (V1) and could be ameliorated by boosting the activity of parvalbumin-expressing interneurons, which are hypoactive in V1 of *Fmr1* KO. To determine how context modifies visual integration in FXS, we used *in vivo* two-photon calcium imaging in head-fixed mice to record network activity in layer 2/3 of V1 to test different mechanisms of visual integration like receptive field size, size and orientation tuning, surround suppression, and adaptation in *Fmr1* KO and Wild-Type (WT) mice. We found that neurons in V1 of *Fmr1* KO mice (n=10) have significantly larger receptive fields than those in WT mice (n=9). We also observed differences in size tuning curves, as larger stimulus sizes (30^o to 60^o) evoked stronger responses (Z-score) in *Fmr1* KO mice than in WT controls. Additionally, genotype differences in orientation tuning were dependent on stimulus size, with larger stimuli (40^o) evoking stronger responses than smaller ones (20^o) in *Fmr1* KO mice but not in the controls. Finally, we found that surround suppression (a type of contextual modulation) also depends on stimulus size, but surprisingly, it was slightly enhanced for smaller stimuli in *Fmr1* KO mice with a significantly lower percentage of Pyr cells responding to the 'iso' stimulus compared to the 'cross' stimulus. Together, our results suggest that atypical visual integration in FXS could be a result of changes in receptive field size and size tuning curves that lead to differences in orientation tuning and surround suppression. Future studies will address whether these changes in size tuning translate into behavioral deficits for *Fmr1* KO mice.

Disclosures: I.A. Tello-Garcia: None. **J. Hsu:** None. **C. Portera-Cailliau:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

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Program #/Poster #: PSTR461.04/G14

Topic: D.06. Vision

Support: NEI R00EY028964

Title: Experience-dependent plasticity to visual stimuli reflects familiarity in mouse anterior cingulate cortex

Authors: *A. MALCI[1], N. HOSAMANE[1], K. WHITTLE[2], M. S. SIDOROV[1,3];
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Park, College Park, MD; [3]Departments of Pediatrics and Pharmacology and Physiology, The George Washington University School of Medicine and Health Sciences, Washington, DC

Abstract: The anterior cingulate cortex (ACC) is a prefrontal brain area implicated in a broad range of functions including cognitive control, attention and prediction in mice. ACC is driven by visual stimuli and is reciprocally connected with visual cortex (VIS). Our previous work demonstrated that visual sequences can be used to drive experience-dependent plasticity in mouse ACC. Here, we recorded visually evoked responses in awake, head-fixed mice that were presented with sequences of four visual stimuli across multiple days of training. We sought to understand whether "sequence plasticity" in ACC reflects familiarity to the first stimulus in a sequence or expectation of the second stimulus. We confirmed that visual sequences drive plasticity in ACC, expressed through a change in the timing of responses, and found that this plasticity reflects familiarity, rather than expectation. We also modified the stimuli in various ways to demonstrate that plasticity reflecting familiarity to individual stimuli can be expressed in the absence of sequences. Combining in vivo recordings with chemogenetic manipulation of VIS-ACC projections revealed that medial secondary visual cortex (V2M) contributes to ACC's function during plasticity. In addition, sensory processing deficits are common in neurodevelopmental disorders including Angelman syndrome (AS), which is caused by functional loss of maternal *UBE3A* gene. Familiarity-driven sequence plasticity is disrupted in ACC, but unchanged in V1, in AS model mice. Our findings in mouse ACC may help to better understand how ACC itself is modulated by experience-dependent plasticity and sensory deficits occurring in individuals with AS.

Disclosures: A. Malci: None. **N. Hosamane:** None. **K. Whittle:** None. **M.S. Sidorov:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

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Program #/Poster #: PSTR461.05/G15

Topic: D.06. Vision

Title: Visual associative learning promotes remodeling of spines in the mouse primary visual cortex

Authors: *M. FARIBORZI[1], L. DEMIR[1], Y. WU[1], M. REHBERG[1], A. RIBIC[2];
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Abstract: Task training results in the formation of new synapses between neurons in the brain, as well as the strengthening of existing ones. These synapses can be visualized as spines, which are protrusions on the dendrites of pyramidal neurons that contain the excitatory postsynaptic apparatus. Longitudinal in vivo imaging studies have demonstrated that spines in the adult cortex are largely stable, but that different types and amounts of training result in their remodeling. For example, motor learning increases spine elimination and formation in the motor cortex. On the

other hand, fear conditioning results in increased clustering of spines in the retrosplenial cortex. However, it is still unclear if the newly formed or clustered spines represent the learned information.
In the primary visual cortex (V1), spines are selective for the orientation of visual cues and are thought to contribute to the orientation selectivity of their host neuron. Previous studies have shown that perceptual learning of orientation cues results in increased spine density in layer 2/3 neurons, but it is unknown if the newly formed spines represent the trained orientations. Thus, we trained adult male and female water-restricted mice on a simple association task where one orientation (120) is paired with a water reward, and the other (240) has no consequence. Mice were injected with AAV-GFP intraventricularly at birth or intracranially with AAV-GCaMP8s 2 weeks before the training started. We then followed the same dendritic branches of layer 2/3 V1 neurons using in vivo 2-photon imaging throughout training, and found that just one training session is sufficient to significantly increase the new spine formation, while existing spines remained stable throughout training. Finally, our longitudinal imaging of spine calcium transients revealed significant changes in the selectivity of spines in layer 2/3 neurons in V1 of trained mice. Altogether, our findings suggest that structural remodeling of connectivity during learning represents the encoding of task-relevant orientations. Our future studies will address the circuit origin of newly formed spines to deepen our understanding of the circuit mechanisms of learning.

Disclosures: M. Fariborzi: None. **L. Demir:** None. **Y. Wu:** None. **M. Rehberg:** None. **A. Ribic:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

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Topic: D.06. Vision

Support: NIH Grant R01EY034644

Title: Maturation of size-tuning in somatostatin-positive inhibitory neurons is delayed relative to classic critical period milestones

Authors: B. B. JEON[1], H. KOBAYASHI[1], M. MOSSO[2], T. FUCHS[2], A. L. BARTH[2], ***S. KUHLMAN**[3,4];
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Abstract: Surround suppression in sensory systems facilitates the processing of complex scenes encountered in the natural environment. To determine whether maturation of surround suppression coincides with the developmental trajectory of classic milestones associated with

visual processing and critical period plasticity in the cortex, size-tuning was assayed in layer 2/3 excitatory neurons of the primary visual cortex in mice using 2-photon calcium imaging. The number of excitatory neurons responding to simple, iso-oriented stimuli was reduced between the ages of postnatal day 28 and 56. This reduction coincided with an increase in the response amplitude of somatostatin-positive (SST) inhibitory neurons to the same visual stimuli. Further analysis revealed that development of surround suppression in excitatory neurons did not reach maturity until postnatal day 56, and that this delay coincided with an increase in SST neuron size-tuning.
We hypothesized that changes in local circuit excitation might underlie the increase in SST activity during these developmental stages. To investigate this, we tagged excitatory synapses onto SST neurons using a Cre-dependent PSD-95 intrabody to compare the size and distribution of PSD95 puncta over time. The density of PSD95 puncta on SST dendrites increased between P28 and P56, consistent with the idea that enhanced synaptic drive onto SST neurons may contribute to the delayed maturation of surround suppression.
These results establish that a key property underlying complex scene processing is not fully mature until well past the closure of the critical period and identifies increased synaptic drive onto SST neurons as a likely contributing circuit mechanism.

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Poster

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Title: Crispr/cas9-based tool reveals contribution of astrocyte-specific gaba transporter, gat-3, to information processing capacity of neurons in the mouse visual cortex

Authors: *J. PARK[1], G. O. SIPE[2], X. TANG[3], P. OJHA[1], G. FERNANDES[1], Y. LEOW[1], C. ZHANG[1], A. NATESAN[1], G. DRUMMOND[1], R. JAENISCH[4], M. SUR[5];
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Abstract: Astrocytes are increasingly recognized as pivotal constituents of neural circuits governing a wide range of brain functions. They express a diverse array of neurotransmitter receptors and transporters, enabling them to monitor and regulate synaptic and neuronal activity. Specifically, astrocytes express a rich repertoire of GABA-related proteins, suggesting they have a role in the regulation of proper inhibitory signaling in brain circuits. GABA transporter 3 (GAT-3) is exclusively expressed in distal astrocytic processes and is the major astrocyte-specific transporter responsible for maintenance of extrasynaptic GABA levels. Here, we have examined the functional significance of GAT-3 in astrocyte-mediated modulation of neuronal activity. First, we developed a multiplexed CRISPR construct applicable for efficient genetic manipulation of one or more genes in a cell-type specific manner with precise temporal and spatial control and tailored this tool to efficiently knock out astrocyte GAT-3 in the visual cortex of adult mice. GAT-3 knockdown was confirmed with immunohistochemistry and whole-cell patch clamp recordings. GAT-3 knockdown increased the frequency of spontaneous inhibitory currents in the visual cortex, indicating an increase in the levels of ambient GABA. We then examined the effects of GAT-3 knockdown *in vivo* using 2-photon calcium imaging of visual cortex neurons. GAT-3 reduction led to alterations in single neuronal responses to drifting gratings and natural movies, including a decrease in maximum response magnitude to preferred stimuli and an increase in response variability. While orientation selectivity of neurons did not change on average, GAT-3 knockout exerted a pronounced influence on population-level neuronal activity, impairing the capacity of neuronal populations to accurately represent stimulus information, as revealed by decoding analyses, and integrate network dynamics, as revealed by encoding models of population activity. These findings demonstrate that reducing GAT-3 in astrocytes profoundly alters the information processing capacity of neurons and networks within the visual cortex. Furthermore, the CRISPR/Cas9-based approach employed here represents a powerful tool for dissecting astrocyte-neuron interactions mediated by different types of neurotransmitters and neuromodulators.

Disclosures: J. Park: None. **G.O. Sipe:** None. **X. Tang:** None. **P. Ojha:** None. **G. Fernandes:** None. **Y. Leow:** None. **C. Zhang:** None. **A. Natesan:** None. **G. Drummond:** None. **R. Jaenisch:** None. **M. Sur:** None.

Poster

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Topic: D.06. Vision

Support: NIH R01EY020950
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Title: Development of binocular integration in the mouse visual cortex after eye opening

Authors: *J. FU[1], S. TANABE[2], J. CANG[2,3];
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Abstract: Stereopsis is the process by which two-dimensional images received by the eyes are integrated to form a representation of the three-dimensional environment, and it originates from disparity selective neurons in the primary visual cortex (V1). While it has been demonstrated that disparity selectivity, like other visual response properties, can be altered by manipulating visual experience during the critical period of postnatal development after eye opening, little is known about how disparity selective circuits function in animals at the start of their visual experience acquisition period, and whether disparity selectivity matures over the course of the critical period with more visual experience. To answer these questions, we performed electrophysiological single-unit recordings in the V1 of awake mice from 0 to 15 days after eye opening (P13 to P30). We presented dichoptic drifting gratings using a polarized projector system. The stimulus set consisted of drifting binocular gratings with varying phase disparity, as well as monocular gratings specific to either eye. We varied the orientation of both binocular and monocular gratings, and all stimulus conditions were interleaved randomly within the stimulus set, which allowed us to reliably measure various aspects of binocular integration without biasing our sample or collecting data affected by adaptation. Neurons in visually naïve mice were less responsive to visual stimulation, with only ~10% of recorded neurons responsive at eye opening, compared to ~50% in adulthood. The degree of selectivity increased in the subsequent 2 weeks towards the adult level. These results indicate that the binocular integrative circuit in mouse V1 exhibits significant changes over the course of postnatal development.

Disclosures: J. Fu: None. **S. Tanabe:** None. **J. Cang:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

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Topic: D.06. Vision

Support: NIH Grant PA-20-185

Title: Functional restoration of PV interneurons alone rescues visual familiarity encoding in Fragile mice

Authors: *S. NAREDDULA, A. A. CHUBYKIN;
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Abstract: Autism is a neurodevelopment disorder that affects information processing in the brain resulting in deficits in sensory processing, social skills, and learning. One of the leading causes of Autism, Fragile X Syndrome (FX), resulting from a single gene mutation on the X chromosome, widely affects the population. In our research we focus on the neural circuit mechanisms involved in visual learning and memory within the primary visual cortex (V1).

Previous research in our lab has shown that visual familiarity induces persistent low frequency 4-8Hz oscillations in the mouse primary visual cortex potentially providing a mechanism for familiarity encoding. Further, disruption of these oscillations results in a loss of performance in a visual discrimination task stressing their importance in visual memory. These oscillations are impaired in FX mice, they are lower in frequency, duration and amplitude. These aberrant features could be due to impaired function of inhibitory neurons, such as parvalbumin neurons (PV), which play a major role in oscillatory circuits and frequency resonance. PV interneurons are structurally and functionally impaired in FX mice. In order to understand the role of PV interneurons in the visual memory circuit and in the context of FX, we used a unique conditional restoration strain, Fmr1cON/PV-Cre, which allowed us to restore FMR1 protein in PV interneurons only. We compared the passive visual learning response in V1 between WT, FX, and Fmr1cON/PV-Cre mice. Our results show that Fmr1cON/PV-Cre mice show improvements in the familiarity induced oscillatory response, with frequency and duration trending towards the WT response. Further, FX mice show a loss in tuning properties post visual familiarity which is rescued in Fmr1cON/PV-Cre mice. In order to understand how this circuit level response translates to behavior, we used an operant conditioning paradigm and analyzed performance to a Go/No-Go visual discrimination task. Fmr1cON/PV-Cre mice performed significantly better than FX mice. These results show that restoration of function in PV interneurons alone is enough to improve circuit level response to familiarity in V1 and improves learning in FX mice. This provides a promising avenue for therapeutic treatment for FX and other ASDs.

Disclosures: S. Nareddula: None. **A.A. Chubykin:** None.

Poster

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RRSV

Title: Orientation responses to precision in the mouse primary visual cortex

Authors: *L. IKAN, J. CAMIL, A. PATALI, M. VANNI, C. F. CASANOVA, N. CORTES; Univ. de Montreal, Montreal, QC, Canada

Abstract: Our research examines the effect of visual stimuli precision on orientation processing in the primary visual cortex (V1) of mice. Our previous findings on cat V1 neurons revealed two main patterns of neuronal response to visual precision: a gradual decrease in activation with diminishing precision, and a consistent response despite changes in precision. These profiles were linked to lateral connectivity in cat V1 neurons, facilitating orientation column selectivity. Here, we explore mouse V1 neurons, which feature a "salt and pepper" organization, lacking the

distinct columnar structure found in cats and primates. Electrophysiological responses were recorded from six anesthetized mice using 32-contact linear electrodes that cover all cortical layers. 'Motion Clouds' (MC), pseudo-natural stimuli, were employed to investigate the effects of orientation precision on neuronal responses. MC stimuli are defined by four parameters: orientation, spatial frequency (SF), Be, and Bsf, with the latter two adjusting MC's precision by modifying the orientation distribution's aperture in the texture. After optimizing neuronal responses to SF and Bsf, ten orientations at five levels of precision were presented, alongside a drifting grating as a control. Orientation tuning at each precision level was analyzed. Out of 418 V1 neurons analyzed, 59% were suitable for analysis, revealing three distinct types of neuronal responses. A significant portion (58%) exhibited a single tuning curve response at the highest precision levels, indicating a preference for finely tuned stimuli. Another group (33%) displayed a broad orientation tuning curve at the highest precision, which then narrowed. Lastly, 9% of neurons maintained a stable response regardless of precision changes. Mouse V1 neurons primarily respond to high visual precision, in contrast to the columnar-based responses observed in cat V1. The "salt and pepper" structure suggests a simpler processing mechanism for high-precision stimuli, advancing our understanding of the complexity and variability in visual processing. Supp : NSERC and RRSV to CC.

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Poster

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Title: Deep learning analysis of visual perception improvement via interneuron subtype transdifferentiation

Authors: *X. HOU[1], Y. LING[2], S. OKUDA[2], S. SUGIYAMA[1];
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Abstract: Freely moving animals interact with environment across a range of situations and choose the best action to take. When they faced with a complex visual discrimination task, some may lead to indecision, whereas others may lead to instead take a direct route without hesitation. However, the role of local circuits within the primary sensory cortex in choosing their action with sensory discrimination is not well understood. The cell-type specific properties and connectivity of cortical inhibitory neurons underlie their ability to spatiotemporally shape information processing. We demonstrated the dendritic transdifferentiation from a specific interneuron subtype to another one improved visual discrimination of behaving animals. These mice were successfully trained to select the correct choice (go or no-go) in response to one grating image (target or non-target) and performance for the correct choice reached over 80 % (no significance between control, 86.6 % and transdifferentiation, 80.8 %). Importantly, in the complex task like two-choice discrimination in which target and non-target images were presented together on both sides of the display, these mice significantly improved their performance compared to control (control, 61.3 %; transdifferentiation, 71.7 %). Tracking mice trajectories revealed how the control mice seemed to come closer to the display and look around for decision-making, whereas the mice with transdifferentiated subtype would instead take a direct route. As a result, both distance and response time to reach the correct choice were significantly shorter in dendritic transdifferentiation phenotype than in control. Further, we found that the number of gazes to display significantly decreases in mice with dendritic transdifferentiation compared to control mice, using the deep learning tool DeepLabCut. Therefore, merely glancing can be enough for these mice to improve visual discrimination ability. Importantly, these mice also become hypersensitive to visual stimulation, demonstrating that the cognitive advantage and hypersensitivity occurs simultaneously. The observed developmental unevenness, resembling features of autism spectrum disorders, may open new avenues for understanding the neural basis of sensory processing and cognitive performance.

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Poster

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Program #/Poster #: PSTR461.12/G21

Topic: D.06. Vision

Title: Female Mice Show Increased V1 Inhibitory Neuronal Activity When Viewing Novel and Familiar Visual Stimuli Compared to Male Mice

Authors: *V. S. INDUGULA, K. JOYCE, R. E. PENTON;
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Abstract: The primary visual cortex (V1) is the first area of visual stimuli integration, perception, and processing in many visual sensory systems. V1 recording data has shown increased inhibitory neuronal activity in mice viewing novel images compared to familiar images

(Garrett et al., 2020). V1 has also shown a correlation between endogenous estrogen and neuronal activity (Jeong et al., 2011). Despite this, female mice remain underrepresented in research, limiting knowledge of sex-specific differences in sensory systems. We explored how sex as a biological variable (SABV) impacts object recognition paradigms in mice models. We examined 2-photon calcium imaging data from the Allen Institute, consisting of V1 area neuronal activity of two mouse models with identified inhibitory neurons; VIP-IRES-Cre x Ai148 and Sst-IRES-Cre x Ai148. An image set was displayed during training, rendering it familiar to the mice during the 2-p imaging sessions, followed by a novel image set (Allen Institute for Brain Science, 2019). We predicted female mice V1 activity would show a greater response to novel images and similar responses to familiar images. After filtering for sex and image type, changes in GCaMP fluorescence over baseline (*dF/F*) traces were analyzed for individual cells. Traces were quantified by their frequency of significant response peaks to measure V1 activity. Regarding sex bias, we found 88% more male experiments within the available data (n=1941) and 93% more within inhibitory genotypes (n=1070). Traces for each cell over 300 seconds were quantified and unpaired t-tests were run between male and female models for both familiar (t=11.51, p<0.0001) and novel (t=2.654, p<0.00081) image experiments. When viewing both novel and familiar images, female mice exhibited a significantly higher amount of inhibitory neuronal activity compared to male mice. Our data suggests inherent sex differences do affect visual stimuli integration within inhibitory V1 experiments for both stimuli types. This implies inherent neurophysiological differences between sexes affecting the integration of visual stimuli. These differences would have gone unnoticed as a consequence of the lack of use of SABV, with visual stimuli processing serving as a way to demonstrate these differences.

Disclosures: V.S. Indugula: None. **K. Joyce:** None. **R.E. Penton:** None.

Poster

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Topic: D.06. Vision

Support: NIH Grant EY030164
NIH Grant EY029245

Title: Binocular interactions in mouse primary visual cortex

Authors: *D. P. MONTGOMERY[1,2], D. BOWEN[3], J. WU[4], M. F. BEAR[5], E. D. GAIER[3]; [1]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC; [2]Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA; [3]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [4]Brandeis Univ., Waltham, MA; [5]Picower Inst. of Learning and Memory, MIT, Cambridge, MA

Abstract: Binocular vision requires that the brain integrate disparate information coming from each eye. Differences in these images are combined to generate a meaningful composite image (fusion) and provide useful information about depth (stereopsis). In some circumstances, interocular disparities are not effectively combined, resulting in diplopia and rivalry. The neural mechanisms underlying normal and pathologic binocular interactions remain poorly understood. Using a combination of visually-evoked potential (VEP) recordings, unit recordings, and 2-photon calcium imaging in the binocular region of mouse primary visual cortex (bV1), we probed the neural mechanisms underlying the processing of two distinct forms of conflicting binocular signals. Using a dichoptic display, we found that introduction of a spatial interocular phase difference in grating stimuli reduced VEP magnitude through decreased neuronal firing in the early phase of the response (40-80 ms after stimulus onset, corresponding to the VEP negativity). Introduction of an interocular orientation difference also decreased VEP magnitude. However, in this case the reduction in VEP magnitude was driven by an *increase* in firing in the late portion (80-200 ms) of the visual response that corresponds to the VEP positivity. From these results, we propose a bV1 circuit model in which interocular phase differences produce suppression via modulation of feedforward thalamocortical interactions, whereas interocular orientation differences produce interocular suppression through disinhibition of feedback responses within bV1.

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Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

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Secretaria de Educacion, Ciencia, Tecnologia e Inovacion de la Ciudad de Mexico

Title: Exploring effects of cortical chandelier cells on the local neuronal network

Authors: *S. PONTES QUERO[1,2,3], T. ALEJANDRE-GARCIA[4,2], R. YUSTE[4,2];
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Abstract: GABAergic interneurons represent a small fraction of all cortical neurons, but show a remarkable genetic, morphological and electrophysiological diversification. This heterogeneity could be associated with specific functions in cortical networks. In spite of this diversity, they share a common neurotransmitter, GABA, which has been shown to be predominantly inhibitory in postsynaptic adult neurons.
Chandelier cells are the single most genetically and morphologically distinct GABAergic interneuron cell type discovered to date. Their highly specific targeting of the axon initial segment (AIS) has been proposed to place them in a privileged position to control the output of excitatory cells. However, several i_n vitro_ studies have suggested that their very specific AIS targeting could also be associated with a potential depolarizing and excitatory effects of this GABAergic synapse due to the specialized array of channel expressed in the AIS which leads to a reversed chloride gradient.
Here we set out to characterize the effect of chandelier cell activation on the surrounding network of excitatory pyramidal cells _in vivo_. To this end we have used the VipR2-Cre line to express ChRmine on chandelier cells while performing 2-photon calcium imaging of excitatory neurons in mouse primary visual cortex. As it has been previously proposed that the effect of chandelier cell could be dependent on the network status, we are carrying out optogenetic activation experiments of single chandelier cells (2-photon) or the local chandelier cell population (1-photon) in spontaneous or visually stimulated conditions. Our results could help elucidate the role of this unique neuron in cortical function.

Disclosures: S. Pontes Quero: None. **T. Alejandre-Garcia:** None. **R. Yuste:** None.

Poster

PSTR461: Visual Cortical Circuits and Modulatory Mechanisms II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR461.15/G24

Topic: D.06. Vision

Support: NINDS Grant RM1NS132981
NEI Grant R01EY035248
NIMH Grant R01MH115900
Ikerbasque Foundation
SECTEI/143/2023

Title: Role of individual chandelier cells in cortical circuits

Authors: *T. ALEJANDRE-GARCIA[1], S. PONTES QUERO[2], R. YUSTE[1];
[1]Columbia Univ., New York, NY; [2]Biol. Sci., Columbia Univ., New york, NY

Abstract: The characterization of the connectivity and the inhibition-excitation synergy of neuronal ensembles is important to understand visual perception. Chandelier cells are a class of cortical interneuron that are anatomically and transcriptomically distinct from other interneuron subtypes. Chandelier cells exclusively innervate pyramidal cells at their axon initial segment, where action potentials are generated. This peculiar anatomical association implies that one chandelier cell could control or modulate the activity of a large number of local pyramidal cells. However, whether this happens, or whether the effect is excitatory or inhibitory is still controversial.We have used a Cre-dependent tdTomato reporter mouse line to identify chandelier cells in the primary visual cortex of Vipr2-Cre mice. To characterize electrophysiological and biophysical properties of chandelier cells, we are performing targeted *in vitro* and *in vivo* patch-clamp. Simultaneously, neuronal population activity is recorded using two-photon calcium imaging. To study how chandelier cell influences pyramidal cell activity at the cellular level, we are exploring the effects of electrical activation and inactivation of individual chandelier cells on the local pyramidal cell population. Our results could help establish the role of chandelier cells in local cortical networks.

Disclosures: T. Alejandre-Garcia: None. **S. Pontes Quero:** None. **R. Yuste:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.01/G25

Topic: D.06. Vision

Support: NIH Grant EY014924
NIH Grant NS116623
Ben Barres Professorship to T.M.

Title: Representations of occluded objects in primate visual cortex

Authors: *S. ZHU, T. MOORE;
Howard Hughes Med. Inst. and Stanford Univ. Sch. of Med., Stanford, CA

Abstract: We perceive objects as permanent despite frequent occlusions. However, the extent to which neurons within the visual system represent occluded stimuli remains elusive. To address this question, we trained macaque monkeys to perform an object permanence task. Subjects tracked a visual object (target) moving across a screen while maintaining fixation. After ~700ms, the target moved behind an occluder and remained stationary and occluded for ~1000ms (OCC condition). Next, the occluder disappeared to reveal an occluded stimulus, which could be the same or different from the original target. Subjects were rewarded for making a saccade to the target if it changed or maintaining fixation if it did not. In ~30% of the trials, the target moved and stopped in the same way except without an occluder; subjects simply reported any visible changes (VIS condition). In both the OCC and VIS conditions, different targets were used,

comprised of natural images or simple shapes. Different initial locations of the target were tested, with varying trajectories that converged to the same occluder location. Monkeys were able to perform the task, demonstrating robust representation of the identity of the occluded objects. We recorded the responses of large populations of neurons in the superior temporal sulcus (STS) (including area MT) using high-density Neuropixels NHP probes. Typically, the occluder's location coincided with the RFs of a substantial proportion of recorded neurons. In each recording, we built firing rate-based decoders from neuronal responses during the stationary target period, for OCC and VIS conditions separately. We found that neuronal populations reliably encoded the trajectory history of targets during the entire stationary period, with similar decoding performance for OCC and VIS conditions. However, decoding of object identity fell to chance levels immediately after full occlusion, despite clear object selectivity during VIS conditions. Our results thus far indicate that neuronal firing rates of STS neurons encode spatial, but not object information during occlusion.

Disclosures: S. Zhu: None. **T. Moore:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.02/G26

Topic: D.06. Vision

Support: National Eye Institute R01EY032878
Simons Foundation (Simons Collaboration on the Global Brain Award 543033)

Title: A systematic comparison of the robustness of pattern and magnitude coding schemes across spikes, LFPs, and high gamma activity

Authors: *C. M. HACKER[1], S. E. BOHN[1], B. G. L. JANNUZI[1], T. MEYER[2], M. L. HAY[2], N. C. RUST[2];
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Abstract: While spiking data collected at high spatial and temporal resolution is the most precise measure of the brain's neural code, the neural signals measurable in human patients (such as LFPs measured intracranially) are often less precise. The consequence of that imprecision for different types of neural codes is not well-understood, but essential for connecting insights from spike data to human patient data. In particular, we know that neural populations rely on at least two types of codes to multiplex information: patterns of spikes (produced by individual neurons with different "tuning preferences") and fluctuations in population magnitude. A classic illustration of this distinction is the representation of orientation versus contrast in early visual cortex. If spatial imprecision amounts from simple averaging of the responses of neighboring

groups of neurons, the expectation is that it will detrimentally impact pattern-of-spike coding while enhancing magnitude coding schemes. To test this prediction, we compared the sensitivity of pattern and magnitude codes in inferotemporal cortex (IT) of three monkeys performing a visual memory task using three types of neural signals: spikes, raw LFP voltages, and high gamma power of the LFP. In IT, patterns of spikes reflect what is being viewed (such as the identities of objects) whereas population response magnitude reflects information about whether an image is novel or familiar. In partial support of the proposal that lower resolution signals reflect the spatial averaging of spike data, we found that for matched numbers of recording sites, raw LFP measures of visual signals in IT were less sensitive than spikes. Likewise, while the sensitivity of high gamma was closer to spikes than raw LFPs, it was still not as sensitive as spike data. However, we also found that the same was true for the magnitude code reflecting visual memory. In that case, we could reliably decode novelty from familiarity from the spiking data collected from each animal, whereas our ability to do so from the LFPs was spurious. These results have two implications for the interpretation of the aggregate signals measurable in human patients. First, aggregate signals should not be interpreted simply as spatially averaged spiking responses. Second, aggregate signals appear to be inherently less sensitive than spikes for both pattern and magnitude coding schemes; consequently, they may not fully reflect all the information present within a brain area.

Disclosures: C.M. Hacker: None. **S.E. Bohn:** None. **B.G.L. Jannuzi:** None. **T. Meyer:** None. **M.L. Hay:** None. **N.C. Rust:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.03/G27

Topic: D.06. Vision

Support: SCGB award 542961SPI
NIH Grant R01EY022930
NIH Grant R01EY034723
NIH Grant RF1NS121913

Title: Learned Associations between Visual Features Reformat Representations to Guide Flexible Behavior

Authors: *A. G. ORWANT[1], R. SRINATH[2], K. D. EAVES[3], M. R. COHEN[2];
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Abstract: When making decisions, we routinely integrate information about disparate features, which often provide correlated but distinct information. For example, deciding whether to eat a blueberry might involve assessing its ripeness via both color and size. Understanding statistical

relationships between information sources, such as a correlation between blueness and size, can help us exploit all available evidence. However, most of our understanding of how brains make decisions comes from experiments that vary a single stimulus feature or the minority of studies that vary two features independently. The neural mechanisms by which correlations between information sources are learned, represented, and incorporated into decision-making remain poorly understood.

We investigated how learned correlations between visual features affect neural representation and decision-making. We first trained a monkey to evaluate the shape and color of two stimuli displayed on the screen and select the more circular one (if the stimuli had the same color) or the bluer one (if the stimuli had the same shape) by making a saccade to it. The stimuli smoothly vary between a triangle and a circle and between white and blue. We simultaneously recorded from a population of neurons in intermediate ventral visual stream area V4 and found a set of neuronal weights defining the linear combination of neurons that best predicted the monkey's choice on each trial. This can be thought of as a "choice axis" in the high dimensional space in which each dimension represents the response of one neuron. We found that this choice axis was stable: a single set of weights could predict the monkey's choices regardless of which feature was task-relevant. We observed that small response modulations reformatted the population responses to align the task-relevant feature with the choice axis.

After achieving threshold performance on both shape and color discrimination trials, we introduced a correlation between the features to study the effect on decision-making. When the two stimuli differed in both features (e.g. a blue circle compared with a white triangle), the monkey incorporated information about both features into the choice. We use these behavioral data and V4 population responses while learning the correlation between stimulus features to test several hypotheses about how relationships between stimuli are encoded in the brain and used to make more efficient decisions. Continuously tracking neural representations while the monkey learns and unlearns different feature associations will illuminate mechanisms by which neural populations enable flexible behavior.

Disclosures: A.G. Orwant: None. **R. Srinath:** None. **K.D. Eaves:** None. **M.R. Cohen:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.04/G28

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Support: Simons Collaboration on the Global Brain award 542961SPI
NIH awards R01EY022930
NIH awards R01EY034723
NIH awards RF1NS121913

Title: Similar signatures of familiarity for action sequences as image sequences in visual area V4

Authors: *L. KRAMER[1], M. R. COHEN[2];
[2]Dept. of Neurobio. and Neurosci. Inst., [1]Univ. of Chicago, Chicago, IL

Abstract: Humans and other animals tend to lump sequences of actions into repeated routines, such as walking to work the same way each time. The psychology literature suggests that visual perception differs while performing novel sequences of actions as compared to familiar routines, even when the stimuli are the same—but the neural mechanisms underlying these perceptual changes remain unknown. Familiarity with an image or a sequence of images has long been known to modulate the responses of neurons throughout visual cortex, including mid-level area V4. In general, single neuron responses are lower for familiar than novel stimuli ('repetition suppression'). We tested the hypothesis that learning a sequence of actions might be associated with similar modulation of V4 responses to what is already a very familiar stimulus. To determine if the findings from a deep set of previous literature about visual learning extrapolate to a much more realistic, subject led behavior, we developed a novel task that balances experimental control and naturalism. We taught rhesus monkeys to move a game piece one space at a time through a familiar two dimensional environment toward a goal. On each trial, we pick the starting location for the game piece and reward location. Monkeys rapidly settle on routine paths from familiar combinations of starting points and goals. Our initial results suggest that :

- V4 neurons exhibit repetition suppression during learning of new action routines, even when the visual stimuli themselves are already extremely familiar,

- and even though the magnitude of responses during familiar routines is reduced, the responses of V4 neurons are more informative about visual features like color and curvature than when the monkey performs an unfamiliar sequences of actions.

Our results suggest that similar mechanisms might underlie modulation of visual responses during learning of images and actions. More broadly, our framework enables future studies of the neural underpinnings of routine learning and its relationship to different aspects of perceptual and cognitive flexibility.

Disclosures: L. Kramer: None. **M.R. Cohen:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.05/G29

Topic: D.06. Vision

Support: Simons Collaboration on the Global Brain award 542961SPI

Title: Behavioral insights into the neural basis of cue combination

Authors: *K. S. ALLEN[1,2], M. R. COHEN[1,2];
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Abstract: Natural behavior requires decision-makers to use many sources of information. In the perceptual realm, basing perceptual judgments on multiple information sources (e.g. perceptual features) is called cue combination. Optimal cue combination entails weighing information sources according to their reliability, making judgments that are more reliable than decisions based on individual features. Neurally, cue combination is thought to be mediated by computations like divisive normalization. Divisive normalization and the balance of excitation and inhibition in the brain are thought to be altered during healthy aging and in disorders that affect perception including attention deficit hyperactivity disorder (ADHD) and Autism, but these differences are difficult to test directly in humans.
We reasoned that we could indirectly test neural hypotheses relating divisive normalization and E/I balance to cue combination by comparing the cue combination behavior of a large, diverse cohort of human subjects. We taught subjects recruited online to perform a perceptual estimation task that required them to make a single direction judgment that combined information from one, two, or three noisy cues (two visual cues: the motion direction and spatial distribution of moving dots, and one auditory cue: the location of a sound). We compared their cue combination behavior to predictions of an optimal Bayesian model and assessed the extent to which they relied on different cues using a cue conflict paradigm in which the different features were consistent with slightly different direction judgments.
We found systematic differences between participant groups by age, or ADHD or Autism diagnosis. All participants were more efficient at combining information from a visual feature with another visual feature than an auditory one. But compared to younger, neurotypical adults, older adults combined cues more optimally within modality than across modalities, while subjects with ADHD showed the most consistent cue combination across conditions. This work highlights the potential for testing neural hypotheses using the behavior of diverse cohorts of human subjects.

Disclosures: K.S. Allen: None. **M.R. Cohen:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

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Program #/Poster #: PSTR462.06/G30

Topic: D.06. Vision

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NIH Grant R01EY034723
NIH Grant RF1NS121913
NIH Grant R24AG073138

Title: Longitudinal measurements of the relationship between visual stimulus properties, visual cortex, and free viewing behavior in a model of Alzheimer's Disease

Authors: *D. SHEETS[1], D. RUFF[1], S. OTT[2], J. KORDOWER[3], S. MULLER[3], J. MORRISON[2], M. R. COHEN[4];
[1]Univ. of Chicago, Chicago, IL; [2]UC Davis, Woodland, CA; [3]Arizona State Univ., Gilbert, AZ; [4]Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Humans and nonhuman primates look around a visual scene 3-5 times per second to gain behaviorally relevant information. A large body of work has characterized the stimulus, cognitive, and neuronal conditions that cause subjects to choose which part of a stimulus to focus on. For example, humans and monkeys both exhibit a preference for viewing novel stimuli compared to previously seen stimuli. Further, models based on free viewing data can predict which parts of a complex image are most likely to be fixated, and these parts of an image elicit characteristically different responses from visual cortex. These known relationships between stimuli, familiarity, visual cortex, and free viewing behavior present an opportunity to advance our basic science understanding of the neural basis of visually guided behavior and its translational potential. Here, we studied a Tau model of Alzheimer's disease (AD) in macaque monkeys (Beckman et al.,2021), which provides a particularly interesting opportunity. Human patients with AD show a decreased preference for novel images and changed patterns of eye movements. And anatomical studies in this model show microscopic changes that affect the ventral visual stream in reverse, with Tau spreading first to inferotemporal cortex and working its way toward primary visual cortex (V1) (Beckman et al.,2021). This makes this model an interesting platform for testing hypothesized relationships between visual neurons and behavior in a very different regime. We recorded longitudinally during Tau progression using chronically implanted microelectrode arrays in areas V1 and V4 while monkeys freely viewed combinations of novel and familiar images. Monkeys fixated a central spot prior to the presentation of two natural images, one of which was positioned over the joint receptive fields of the recorded neurons. When the fixation point disappeared, monkeys were rewarded for freely viewing either or both stimuli for at least one second. Our initial results suggest that, as in human AD patients, novelty preference decreases relatively late in disease progression. However, we were able to detect changes in visual neurons and in different measures of free viewing behavior much earlier. These results suggest that using an AD model of visual cognition holds promise for 1) basic science goals of testing models of the relationship between stimuli, familiarity, visual cortex, and free viewing behavior in a different regime than most experiments and 2) translational goals identifying aspects of visually guided behavior that could be useful for early detection of AD in people.

Disclosures: D. Sheets: None. **D. Ruff:** None. **S. Ott:** None. **J. Kordower:** None. **S. Muller:** None. **J. Morrison:** None. **M.R. Cohen:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Program #/Poster #: PSTR462.07/G31

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Support: Simons Collaboration on the Global Brain award 542961SPI
NIH R01EY022930
NIH R01EY034723
NIH RF1NS121913
NIH R24AG073138

Title: Linking visual neurons to behavior in a longitudinal model of Alzheimer's disease

Authors: *D. A. RUFF[1], S. OTT[2], S. MULLER[3], J. H. KORDOWER[3], J. H. MORRISON[2,4], M. R. COHEN[1];
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Abstract: For both translational and basic science reasons, the ability to measure behavior and neural activity longitudinally in disease models could transform our ability to link the activity of neurons to behavior. For basic science, disease models can provide causal manipulations of cognitive processes that are difficult to achieve through other methods. Translational efforts to diagnose and treat disorders of cognition are in desperate need of new approaches and might benefit from the body of basic knowledge in fields like the neural basis of visually guided behaviors.

Here, we use a recently developed Tau model of Alzheimer's disease in macaque monkeys (Beckman et al., 2021) to investigate the time course of behavioral and neuronal response changes during Tau progression. An adeno-associated virus expressing a double tau mutation (AAV- P301L/S320F) was injected bilaterally into entorhinal cortex, which leads to the progressive spread of pathologic Tau proteins throughout the brain at a rate that is inversely proportional to anatomical distance from entorhinal cortex. Of particular interest is that Tau spreads backwards through the ventral visual stream, affecting inferotemporal cortex and later areas V4, V2, and then V1 (Beckman et al, 2021). This makes it possible to test theories from our lab and others affecting visual cortical activity with different behaviors and to identify visually guided behaviors that might be useful for early diagnosis. We made daily recordings from areas V4 and V1 using chronically implanted multielectrode arrays while monkeys performed a selection of visually guided tasks. These data allow us to measure changes in neural activity and in different visually guided behaviors during different phases of disease progression, associated first with changes to downstream areas (and therefore feedback to V4 and V1) and later combined with direct changes to those areas themselves.

Our initial results suggest that the early phase of Tau progression is associated with changes in both the private and shared response variability of visual neurons that precede clear behavioral deficits. Later in disease progression, we see qualitatively different neural population responses which are accompanied by changes in various behavioral measures associated with eye movement planning, preference for novel images, and distractibility. Interestingly, these changes seem linked to measures of the neural population response (shared variability, dimensionality, etc.) and are not accompanied by changes in information coding. Our approach provides a

blueprint for accomplishing basic science and translational goals in a complementary, interconnected way.

Disclosures: D.A. Ruff: None. **S. Ott:** None. **S. Muller:** None. **J.H. Kordower:** None. **J.H. Morrison:** None. **M.R. Cohen:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.08/G32

Topic: D.06. Vision

Support: NIH COBRE awd-01-00002341

Title: Different tasks performed on same objects result in functionally distinct activation of LOTC and IPS

Authors: *A. BISWAS[1], M. D. LESCROART[2];
[1]Univ. of Nevada, Reno, Reno, NV; [2]Psychology, Univ. of Nevada Reno, Reno, NV

Abstract: Humans interact with the same objects in different ways based on the task at hand, and correspondingly, brain responses to the same objects can be modulated by task demands. Flexible perception is thought to rely on a network of areas termed the Multiple Demand Network (MDN), spanning parts of the parietal, frontal, and lateral occipital cortex. Here, we investigate the degree of functional specificity vs domain generality among regions in the MDN. To this end, we constructed an fMRI experiment in which human participants made judgments using different features of the same object. For each trial, participants either passively fixated or indicated whether a) medial axis structure or b) set of local shapes comprising the object or c) object texture was different from that of the previous object. Performing multiple tasks while presenting the same stimuli allows the study of task-specific responses independent of the stimuli. We created an encoding model with indicator variables for task conditions to derive weights associated with each task for every voxel. This model explained unique variance in a withheld portion of the dataset over and above stimulus-based models in regions of the frontal, parietal, and lateral occipital cortex. Principal Component Analysis of task weights across task-selective voxels revealed that less than half the variance was explained by a component indicative of activation across all tasks. Furthermore, contrast analysis of weights pointed to a significant number of voxels more tuned to specific tasks as opposed to uniform activation across all three tasks. Among these regions, we found that posterior LOTC ventral to hMT+ and dorsal to OFA responded more in the local shape task. A region just anterior to this responded more in the medial axis task. The texture task engaged more posterior regions. We also found spatially distinct activations in the IPS for different tasks. Although these varied across participants, some regions including lateral IPS were reliably activated by the medial axis task. These results point

towards functional specificity of regions within the MDN, with different regions representing relatively more global and local aspects of object shape.

Disclosures: A. Biswas: None. **M.D. Lescroart:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Program #/Poster #: PSTR462.09/G33

Topic: H.05. Working Memory

Support: ERC-2020-COG 101000972

Title: Abstracted Representation of Object Orientation During Working Memory in Primary Visual Cortex

Authors: *O. YIZHAR, B. SPITZER;
Max Planck Inst. for Human Develop., Berlin, Germany

Abstract: Visual Working Memory (WM) storage has been linked to a multitude of areas in the human brain, including early visual cortices. Despite this, there is currently no consensus on which roles the different cortical regions play in WM storage. In the present study, we used a new approach to characterize the nature of WM representations in the primary visual cortex (V1). During fMRI scanning, participants (n=40) were asked to remember rotated objects in a retro-cued WM task. The visual objects differed in their semantic and physical characteristics but shared a feature space in terms of abstract orientation (Fig. 1a). Using representational similarity analysis, we inferred the level of abstraction of orientation representations from the extent to which they generalized across physically dissimilar images. Specifically, we compared the strength of orientation encoding within vs. between dissimilar objects (Fig. 1b). Applying this analysis approach to multivariate voxel patterns in bilateral V1, we found robust encoding of the cued object orientation during the WM retention period (Fig. 2a), both within and between objects (Fig. 2b). Critically, orientation encoding within and between objects was similarly strong, indicating that the orientation representation in V1 was in an abstract format. The results provide new evidence for the hypothesis that WM can maintain an abstract format of low-level perceptual features, such as orientations, even in early sensory cortices.

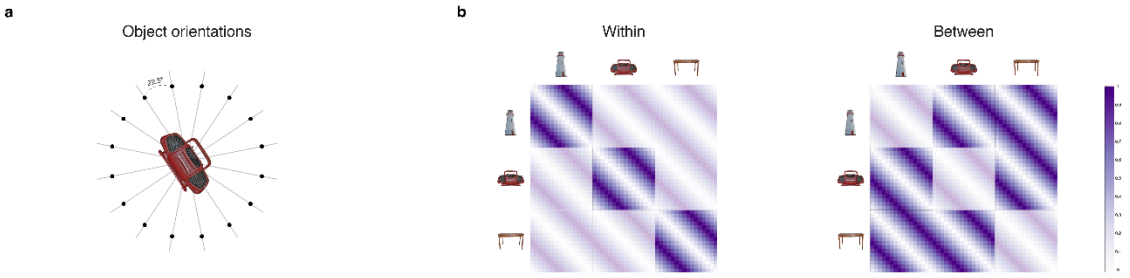

Figure 1. (**a**) During the working memory task, participants were required to remember a visually oriented object. Each object appeared in 16 different orientations. Each object was presented in 16 different orientations. (**b**) Representational dissimilarity structures for orientations. The left panel illustrates orientation distances within each object. The right panel displays orientation representational distances measured between different objects. Utilizing these two models, we can infer whether objects were stored in working memory in abstract or concrete formats

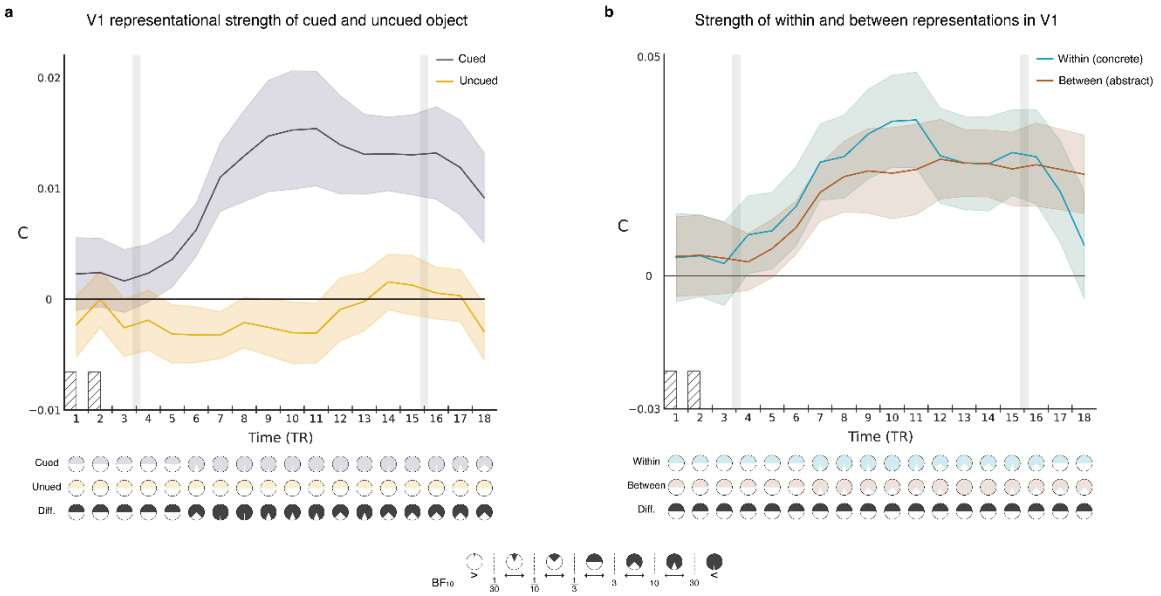

Figure 2. Timepoint-by-timepoint RSA orientation encoding in V1(n=40). The striped boxes depict the timings of visual objects during encoding. The gray vertical lines indicate the retention period of the WM trial from the retrocue (TR=3) until the recall test (TR=15) (**a**) During WM retention, the representational strength of the cued object significantly exceeds that of the baseline and the uncued object. (**b**) For the cued items, encoding of orientation representations was robust when measured within objects and between objects, with no significant differences observed between them. Each pair of rows at the top presents the Bayes Factor score for a two-sided tests against a null hypothesis, while the bottom row displays the scores for the pairwise comparison between the two lines. Shadings at each time point indicate the standard error of the mean (SEM). C denotes cosine similarity.

Disclosures: O. Yizhar: None. **B. Spitzer:** None.

Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

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Program #/Poster #: PSTR462.10/G34

Topic: D.06. Vision

Support: 1R01EY031589-01

Title: Experience-dependent plasticity in adult human brain following visual perceptual training: a pilot study.

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Abstract: Macular Degeneration (MD) is retinal pathology affecting photoreceptors in the central portion of the visual field. Deprived of a functioning fovea, patients often use a new eccentric fixation area that includes a spared peripheral portion of the retina (preferred retinal locus - PRL) to perform fine-scale viewing tasks, such as reading, navigating and recognizing faces. Mechanisms of development of the PRL are still elusive, with studies suggesting that it is not necessarily the region in the spared retina with the highest resolution. MD represents an ideal model for studying experience-dependent plasticity in the adult human brain. Specifically, we used a gaze-contingent display approach to simulate MD in healthy individuals, as simulated scotoma is becoming an increasingly common framework for the study of eye movements and visual training effects in MD without the practical constraints typical of studies with clinical populations. We assigned a “PRL location” to the right or left visual field in the horizontal axis of the central vision to each participant. All healthy participants conducted twenty visual training sessions targeting low, intermediate, and high-level visual processes, and they underwent baseline and post-training MRI assessments. In each MRI assessment, participants completed a total of six runs of orientation discrimination and contour integration tasks. We assessed both behavioral and BOLD activity change during the tasks before and after visual training. Our results indicate that both accuracy and reaction time improved in the post MRI session compared to baseline. In addition, in line with the literature, we observed a reduction in overall active voxels and BOLD activity in the post MRI assessments compared to baseline MRI session. The observed training-related decreases could be associated with increased neural efficiency in these specific cortical correspondences of the trained and untrained areas for the task performance. We discuss how baseline behavioral performance/neural activity in right or left loci might be related to performance/activity in the trained location as well as potential PRL location selecting strategies. Our study contributes to the understanding of PRL location selection strategies as well as the broader topic of experience-dependent brain plasticity in healthy adult brains.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR462.11/G35

Topic: H.10. Human Learning and Cognition

Title: Associative learning influences representational structure of objects in the ventral visual pathway and hippocampus

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Abstract: The ventral visual pathway is an object processing hierarchy that enables adaptive behavior by mapping visual input (e.g., shape) onto semantic knowledge (e.g., function). Neuroimaging and lesion studies have revealed the representational properties of numerous structures within this pathway, with particular emphasis on lateral occipital cortex (LOC), fusiform gyrus (FG) and perirhinal cortex (PRC), which have been linked to coding of visual and/or semantic object properties. The role of these structures in representing visual information and semantic knowledge is thought to be distinct from the role of the hippocampus (HPC) and parahippocampal cortex (PHC), which captures arbitrary contextual associations in service of episodic memory. Here, we asked whether and how learning arbitrary associative structure among visually or semantically similar objects influences how they are represented in the ventral visual pathway, PHC, and in the HPC. We addressed this question using functional magnetic resonance (fMRI) in cognitively healthy humans. On day one, participants completed a scanned 1-back task using images of objects that were either visually similar (e.g., tennis ball and lime), semantically similar (e.g., tennis ball and tennis racquet), or unrelated (tennis ball and saxophone). We used a representational similarity analysis to fit behavior-based models that separately captured the visual and semantic similarity structure of the objects to neural similarity structure in targeted ventral stream regions, as well as PHC and the HPC. This approach revealed concurrent visual and semantic coding of objects in FG and LOC, and visual coding of objects in PRC. Neural similarity structure on day one could not be explained by visual or semantic properties in either PHC or the HPC. On days two and three, participants learned arbitrary associations among objects (i.e., triplets with limited visual and/or semantic similarities). On day four, participants completed a second scanned 1-back task, which allowed us to characterize learning-related changes in the representational structure of our targeted areas. This approach revealed learning-related changes in all regions examined. Specifically, objects from each triplet were more similar to one another after learning than before. Interestingly, this shift came at the expense of the representational structure expressed prior to learning in FG, but not in either LOC or PRC. This pattern of results suggests that ventral stream structures are sensitive to arbitrary associative structure and that this information can be embedded in a complex signal that also captures inherent stimulus properties.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Topic: D.06. Vision

Support: European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant agreement No. 802482, named "VarPL")
Studienstiftung PhD fellowship
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Title: Visual perceptual learning improves orientation decoding while reducing BOLD amplitude in V1 and V2

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Abstract: The adult visual system can respond to new environmental challenges through plasticity, a process known a visual perceptual learning. While behaviorally well characterized, the neural mechanisms underlying this form of plasticity remain a matter of debate. In particular, human functional magnetic resonance (fMRI) studies have reported changes in amplitudes of evoked evokes responses in early visual cortex as well as changes in the amount of task-relevant information, inferred from multivariate decoding. While changes in amplitudes have been interpreted as improved efficiency of sensory encoding, how this efficiency relates to changes in task-relevant information, if at all, remains unclear. Here, we address both proposed mechanisms concurrently in the context of orientation discrimination learning.We trained healthy human adults (n=12) for four days with an orientation discrimination task in the upper left visual field and collected fMRI data before and after learning. We analyzed BOLD amplitude changes (percent signal change) and orientation decoding accuracy in retinotopically defined regions of interest representing the stimulus location in V1, V2, and V3. Behaviorally, participants improved their performance in orientation discrimination task. BOLD amplitudes reduced in all three regions, while decoding performance of orientation information increased with learning in V1 and V2 only. The changes in amplitudes were uncorrelated to the changes in decoding in V1 and V2.Taken together, our data show that perceptual learning results in amplitude reductions in parts of early visual cortex, suggesting more efficient processing. In addition, more stimulus information becomes available for readout, as identified in the multivariate analyses. Given that the two learning-related changes are uncorrelated and fully dissociated in V3, this suggests that perceptual learning concurrently but independently optimizes metabolic demands and information processing.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

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Program #/Poster #: PSTR462.13/G37

Topic: D.06. Vision

Support: European Research Council (ERC-2019-COG 866093)
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Ariane de Rothschild Women's Doctoral Program

Title: Distinct neural mechanisms enhancing visual perception and enabling learning generalization

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Abstract: The acquisition and improvement of skills are essential for daily function. A fundamental example is perceptual learning, which can significantly improve visual sensitivity. However, such improvements commonly require extensive stimuli exposure. Here, we present evidence that distinct neural mechanisms can improve visual perception, with remarkably enhanced efficiency utilized by minimizing stimuli exposure. Participants encoded a visual discrimination task, followed by brief memory reactivations of only five trials each performed on separate days, demonstrating learning gains (mean 24.7% ± 4.1% SE) comparable ($p=.90$, $BF_{01}=3.22$) to standard repetition-based learning (252 trials per session; 25.4% ± 3.9%). Reactivation-induced learning was associated with increased bilateral intra-parietal sulcus activity relative to repetition-based learning. Additionally, changes in temporal-parietal resting functional connectivity provided complementary evidence for differential learning processes, which correlated with behavioral improvements. To further evaluate these novel mechanisms, microstructure differences are now examined using diffusion tensor imaging (DTI). Furthermore, while standard repetition-based perceptual learning typically exhibits strong specificity to the trained stimulus features, preliminary evidence implies that such increased engagement of higher-order brain regions in reactivation-induced learning facilitates learning generalization. Such generalization is often a highly desirable outcome of the learning process, promoting learning efficiency beyond the specific trained features. The results suggest that efficiently enhancing visual perception with minimal stimuli exposure recruits distinct neural processes, engaging higher-order control and attentional resources, while leading to similar perceptual gains and enabling learning generalization. These findings shed light on unique mechanisms underlying efficient learning and may hold important implications for daily life and in clinical conditions.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Topic: D.06. Vision

Support: K99 HD099203-01 "The neurodevelopmental mechanisms linking environmental experience and executive function"

Title: Mapping Young Minds: Multivariate Pattern Analysis of Children's Ventral Occipital temporal responses to Categorized Visual Stimuli and Socioeconomic Influences

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Abstract: Ventral Occipital-Temporal cortex (VOTC) is involved in complex visual processing, specifically containing specialized regions that process distinct categories of information (Kanwisher et al., 1997; Epstein et al., 1999). Visual processing can be of great importance as previous studies in children have found that socioeconomic status (SES) is positively correlated with neural activation in the ventral visual stream (VVS) when children perform a cognitively demanding task. Such association is mediated by the cognitive stimulation in the home, which is defined as caregiver involvement in learning, access to learning materials, exposure to complex language, and experiencing a variety of activities. It remains unknown whether these associations exist during basic visual processing. We seek to extend previous research by testing the hypothesis that there are adult-like distinct brain activity patterns for different image categories in children but that these patterns vary as a function of SES, children's cognitive stimulation and executive function performance. We employ multivariate pattern analysis support vector machines to classify children's fMRI data collected when they are viewing images of 8 categories. We then fit the linear regression model with SES, cognitive performance, and cognitive stimulation variables and the average decoding accuracy. This study advances our knowledge on children's visual processing and the impact of the environment such as SES and cognitive stimulus on its development.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Topic: D.06. Vision

Support: The Scientific and Technological Research Council of Türkiye (ARDEB Grant 121K251, BIDEB 2211 Program)

Title: Exploring the integrated effects of transcranial random noise stimulation and visual perceptual learning: insights from the perceptual template model

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Abstract: Visual perceptual learning (VPL) and transcranial electrical stimulation (tES) are promising non-invasive interventions aimed at enhancing perceptual performance. VPL is defined as the improvement in the performance of a perceptual task induced by practice (Lu & Dosher, 2022). Conversely, tES is a non-invasive technique that utilizes weak electrical currents to modulate neural activity in the brain. Among the various tES methods, transcranial Random Noise Stimulation (tRNS) is noteworthy due to its effectiveness in enhancing visual perception (van der Groen et al., 2022). Recent research has concentrated on the combined application of these methods (Maniglia, 2022) to elucidate the neuromodulatory effects of tES on VPL. However, research examining the effects of sequential multi-day tRNS on VPL procedures remains scarce. Employing the Perceptual Template Model (PTM) as a theoretical framework could deepen our understanding of the synergistic application of these methods, thereby unveiling the cortical mechanisms of VPL modulated by tRNS. In this study, we administered online high-frequency tRNS (hf-tRNS) bilaterally over the human medial temporal complex (hMT+, n=12) to modulate motion processing during perceptual training sessions conducted on six consecutive days. To evaluate the specificity of hf-tRNS, we included both sham (n=11) and a control stimulation site (M1) (n=10). We assessed contrast sensitivities (CS) across a range of external noise levels, which were measured before, during, and after VPL to uncover the mechanisms of electrical neuromodulation. The results showed the efficacy of the VPL, as evidenced by the enhancements in CS across all groups. We further explored the patterns of CS modulation through PTM across groups. The model results provided valuable insights into the mechanisms of VPL modulated by tRNS, from both internal and external noise perspectives. Specifically, signal enhancement and external noise exclusion emerged as mechanisms of VPL in both control groups. In contrast, the PTM did not favor any specific noise reduction mechanisms to account for the training effects observed during tRNS over the hMT+ area. These findings suggest that hf-tRNS may limit the underlying mechanisms of VPL-modulated noisy perceptual templates in motion processing. Given that the practical applications of VPL in clinical populations are constrained by the lengthy duration required for significant improvement (often weeks to months), our findings could inform more efficient applications of tES in VPL training protocols.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Program #/Poster #: PSTR462.16/H3

Topic: D.06. Vision

Support: NIH Grant R01EY35533
NIH Grant R01MH122258

Title: Single pulse white matter stimulation modulates neural responses in human visual cortex.

Authors: *D. HERMES[1], H. HUANG[2], N. GREGG[3], G. OJEDA VALENCIA[2], B. N. LUNDSTROM[1], M.-H. IN[4], J. HUSTON[1], Y. SHU[1], E. GRAY[1], D. KANG[1], G. A. WORRELL[1], K. J. MILLER[5], K. N. KAY[6];
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Abstract: Electrical stimulation is increasingly used to modulate brain networks for clinical purposes. Electrical pulses can interact with natural neuronal processing in connected networks, and previous studies suggest that electrical stimulation produces brief excitation followed by inhibition. The visual system provides a unique opportunity to better understand how electrical inputs interact with neuronal processing. In two human subjects implanted with stereo EEG (sEEG) electrodes for clinical purposes, single electrical pulses were delivered to a pair of electrodes placed in white matter tracts connecting to early visual areas (the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus). Stimulation was delivered at various electrical-visual intervals (EVIs) before the onset of a visual image (-200 ms, -100 ms, 0 ms and sham stimulation). In sEEG electrodes in V1-V3, we calculated time-varying broadband responses and visual evoked potentials. Each type of signal was modeled using a set of finite impulse responses over time, which allowed us to separate stimulation-evoked and visual-evoked responses. Broadband power exhibited a brief increase after electrical stimulation, followed by subsequent suppression, but stimulation did not change the visual broadband response in an EVI-dependent manner. Interestingly, visual evoked responses varied based on EVI: evoked potentials were larger in amplitude when stimulation was delivered at 0 or 100 ms before image onset, compared to sham stimulation or stimulating 200 ms before stimulus onset. Stimulation of control sites (not located in connected white matter tracts) did not produce these effects. These results suggest that the network effects of single pulse electrical stimulation change rapidly over time, facilitating evoked activity only for a brief period after stimulation.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

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Program #/Poster #: PSTR462.17/H4

Topic: D.06. Vision

Support: NRF Grant 2022R1A2C3008991

Title: Inherent receptive fields in the early visual pathway for robust continual learning

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Abstract: Continually learning new information is an essential ability of animals (Kudithipudi et al., 2022), but posing a challenge for conventional deep neural networks (DNNs). When DNNs undergo training in different domains, they tend to forget previous information, which is called catastrophic forgetting (McCloskey & Cohen, 1989). Yet, the mechanisms producing such a functional difference between DNNs and brains remain elusive. In contrast to DNNs, whose early layers are initialized with random filters and trained based on the dataset, the early visual pathway of the brain exhibits inherent Gabor-like receptive fields (Ringach, 2002; Paik & Ringach, 2011) that remain stable throughout a lifetime (Godecke et al., 1997). Here, we propose that pre-developed Gabor filters in the early layers of DNNs, akin to the primary visual cortex (V1) cells' receptive fields, enable continual learning under dynamic domain changes. To test our idea, we modeled V1 neurons' receptive fields as Gabor filters, incorporating them as filters of the first convolutional layer of DNN (Krizhevsky et al., 2012) to simulate the biological visual systems. We then sequentially trained networks using two distinct image domains, Photo and Sketch images, which exhibit pronounced differences in low-level features such as spatial frequency. As a result, we found that conventional DNNs completely lost the performance of the first domain when trained on a different domain, showing catastrophic forgetting. Conversely,

DNNs with fixed Gabor filters successfully maintained their previous performance even when trained on a new domain. This phenomenon persisted across various domain pairs beyond Photo and Sketch images, underscoring the effectiveness of fixed Gabor filters under general variations of input domains. Next, to elucidate the mechanisms underlying the maintained performance of our model, we examined the internal layer representations of Photo and Sketch images. We found that our model has more clustered representations of the same classes across different domains (e.g., Photo dogs and Sketch dogs) than DNNs, which may lead to enhanced adaptability in a continuously changing environment. These results may indicate the potential advantage of fixed Gabor filters as universal feature extractors regardless of diverse domains. Collectively, Gabor filters in early layers can function as pivotal architectures for continuous learning, highlighting the functional importance of stable early visual pathways observed in biological brains.

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Poster

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Title: A Visual Behavioral Study of Categorical Face Pattern Recognition in Mice

Authors: *Y. CHEN[1], L. GUO[2], R. JIANG[2], K. ZHOU[3], X. ZHAO[2], M. MENG[1];
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Abstract: The advantage in face perception over other stimuli is well established in humans and several animal species, yet the extent to which mice manifest similar behavior remains unclear. To address this question, we randomly divided 16 wild-type (WT) mice into two groups of eight: one trained with human face pictures and the other with mouse face pictures. Both groups underwent training tasks to differentiate between face and control object pictures across daily 30-minute sessions involving up to 60 trials. Pictures presented in a single trail were balanced for brightness, contrast, and spatial frequency. Mice that achieved over 75% accuracy on the training task for two consecutive days proceeded to testing phase. The testing phase introduced novel stimuli without reward cues, including new upright and inverted faces as well as contrast negated

face pictures. We established generalized linear mixed-effect models (GLMMs) for data analysis with 'binomial' as the link function. In two GLMMs comparing task accuracy (ACC) between picture types and chance levels for human and mouse face training groups, we found that mice are able to discriminate between new face pictures and objects (Human face: *Mean ACC*=0.604,$P<0.001$; Mouse face: *Mean ACC*=0.559,$P\leq0.01$. By contrast, performances on inverted (Human face: *Mean ACC*=0.537, *P*=0.132; Mouse face: *Mean ACC*=0.532, *P*=0.152) and negative (Human face: *Mean ACC*=0.504, *P*=0.884; Mouse face: *Mean ACC*=0.535, *P*=0.124) pictures were not significantly different from chance levels, suggesting a disruption of face processing similar to humans. To explore whether mice have formed a human-like categorical perception of faces, in Experiment 2 we further tested non-face pictures with varying degrees of resemblance to human faces based on human ratings of face-like attributes, serving as a measure of face perception capabilities, and constituting an indicator of categorical face representation. We established similar GLMMs. Mice exhibited no significant difference in the performance on high-similarity human face tasks compared to actual face tasks (*Z*=-1.144, *P*=0.253) but showed significant differences in the low (*Z*=-2.822, *P*=0.005) and medium-similarity (*Z*=-2.845, *P*=0.004) face tasks, indicating that mice might form categorical face perception similar to humans. These findings elucidate aspects of the cognitive mechanisms underlying face pattern recognition in mice and set a foundation for future electrophysiological explorations, offering insights into both psychological and biological aspects of face perception.

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Poster

PSTR462: Visual Learning, Memory, Decision-Making, and Effects of Brain Stimulation

Location: MCP Hall A

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Program #/Poster #: PSTR462.19/H6

Topic: F.01. Neuroethology

Support: Margarita Salas Fellowship

Title: Thoughtful Faces: Facial features reveal similar cognitive states in monkeys and mice

Authors: A. TLAIE BORIA[1], M. ABD EL HAY[1], B. MERT[2], R. TAYLOR[1], K. SHAPCOTT[1], M. GLUKHOVA[1], J. W. PILLOW[3], M. L. SCHÖLVINCK[1], *M. N. HAVENITH[4]; [1]Ernst-Strüngmann Inst. for Neurosci., Frankfurt am Main, Germany; [2]Max Planck Inst. for Psychiatry, Munich, Germany; [3]Princeton Univ., PRINCETON, NJ; [4]Ernst Strungmann Inst. For Neurosci., Frankfurt Am Main, Germany

Abstract: Animal behaviour is strongly shaped by spontaneously fluctuating cognitive states such as motivation and attention, but it is unknown to what extent such internally driven states translate across species. To address this question, we developed a virtual reality paradigm that allows mice and macaques to engage in an identical naturalistic visual foraging task. We then

used a wide range of facial features extracted from video recordings before each stimulus presentation to train a Markov-Switching Linear Regression (MSLR). In this way, we identified, on a single-trial basis, a set of internal states that reliably predicted when animals were going to react to each upcoming stimulus. Even though the model was trained purely to predict reaction times, the inferred internal states also predicted task outcomes, indicating their behavioural relevance. The identified states were comparable between mice and monkeys, but mice switched between states more dynamically. Finally, each internal state corresponded to a characteristic pattern of facial features, highlighting the importance of facial expressions as multi-faceted manifestations of internal cognitive states across species.

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Poster

PSTR463: Basal Ganglia: Systems Behavior II

Location: MCP Hall A

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Program #/Poster #: PSTR463.01/H7

Topic: E.03. Basal Ganglia

Support: NSF GRFP
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RF1NS132913

Title: Selective contribution of striatal indirect pathway neurons to reduced movement vigor

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Abstract: Determining how vigorously to perform a movement depends critically on neural circuits in the striatum, and their modulation by dopamine. Two subtypes of spiny projection neurons (SPNs) in the dorsal striatum, the direct pathway SPNs and indirect pathway SPNs, are key targets of dopamine and thought to be particularly important for vigor modulation. The direct pathway SPNs express dopamine D1 receptors (D1+) while indirect pathway SPNs express dopamine D2 (and adenosine A2a) receptors (A2a+), and are hypothesized to facilitate and inhibit movement, respectively. However, this is now controversial since D1+ and A2a+ neurons have been found to be coactivated during movement initiation and execution. We are monitoring the firing of optogenetically identified D1+ and A2a+ neurons from the dorsomedial striatum (DMS) and the dorsolateral striatum (DLS) in unrestrained rats performing a trial-and-error task (Hamid et al. 2015). In this task, rats adjust their response vigor (reaction time, RT) to a *Go!* cue according to the reward probability for their chosen leftward or rightward movement

into an adjacent hole. At this time, we have recorded: n=187 DMS D1+; n=373 DMS A2a+; n=60 DLS D1+; and n=355 DLS A2a+ neurons. We found movement-related activity among all four neuron classes. However, selectively in DLS A2a+ neurons, we found positive correlations with RT. This would be consistent with a distinct A2a+ function in reducing the vigor of movements. The preferential involvement of DLS over DMS in influencing RT is consistent with dopamine measurements in the same task (Mohebi et al. 2024) where greater *Go!*-evoked DA is associated with shorter RT. We are continuing to investigate and compare the contributions of D1+ and A2a+ neurons across the dorsal striatum using both recording and optogenetic manipulations.

Disclosures: I. Gonzalez Montalvo: None. **M. Duhne:** None. **L. Pelattini:** None. **J.D. Berke:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.02/H8

Topic: E.03. Basal Ganglia

Support: NIH grant R01NS123516
NIH grant R01DA045783
PEW Charitable Trusts

Title: Spiking of identified parvalbumin-expressing interneurons in dorsal striatum is consistent with preventing premature actions.

Authors: *M. DUHNE[1], J. D. BERKE[2];
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Abstract: The dorsal striatum has a central role in the selection and invigoration of actions. Although >90% of striatal neurons are spiny projection neurons (SPNs), the remaining interneurons are thought to strongly influence striatal information processing. However, the functions of specific striatal interneuron classes remain poorly understood, in part because it has proven very challenging to record from identified striatal cells in behaving animals. In ongoing studies we have been using optogenetic tagging to successfully monitor the spiking of two major classes of GABAergic interneurons in dorsolateral striatum: parvalbumin-expressing (PV+; n=30) and somatostatin-expressing (SST+; n=13). Unrestrained rats performed a trial-and-error decision-making task (Hamid et al. 2016), which involved maintaining a nose-poke for an extended period (500-1500ms) while waiting for a Go! cue. Identified DLS PV+ cells had consistently high firing rate (mean 13.3 Hz) and relatively brief waveforms. To our surprise, however, they did not correspond to the fast-firing cells with very brief waveforms that we and others have previously presumed to be PV+. Task-related activity of PV+ cells was also unexpectedly consistent, with ~80% of these neurons showing elevated activity during the hold

period with a sharp decrease immediately after the Go! cue. Optogenetic activation of PV+ cells reduced activity of nearby presumed SPNs. We suggest that the elevation of PV+ cells during the hold period may help restrain impulsive actions through suppression of SPNs, consistent with prior suggestions for ventral striatum (Pisansky et al. 2019). Unlike PV+, identified SST+ neurons did not show consistent firing rate or waveform properties, and did not show consistent relationships to task events, although we have a limited number so far. Stimulation of SST+ neurons caused an increase in the firing of presumed SPNs, consistent with dis-inhibition. Overall, this study is beginning to reveal unexpected properties of striatal GABAergic interneurons, that will inform new models of striatal microcircuit operations and functions.

Disclosures: M. Duhne: None. **J.D. Berke:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.03/H9

Topic: E.03. Basal Ganglia

Support: NIH F31

Title: Investigating the contributions of spiny projection neurons within the tail of striatum in filtering task relevant auditory stimuli

Authors: *S. M. FERRIGNO, N. ZHANG, M. V. FUCCILLO;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: The basal ganglia are a series of interconnected nuclei which filter and amplify forebrain excitatory inputs to align context-dependent motor output with reward. An initial stage of this processing is thought to occur via synaptic regulation of cortical projections to the striatal direct and indirect pathways, which serve to amplify task relevant cortical representations and dampen less relevant competing representations, respectively. Recent work has demonstrated auditory cortical inputs to the tail of striatum are required for auditory guided decision-making with optogenetic manipulations of direct/indirect spiny projection neurons (d/iSPNs) sufficient to bias auditory guided choice. Furthermore, dopaminergic signaling within the tail has been observed to mediate perceptual aberrations in mice. Taken together, these data support a role for the tail of striatum in auditory guided decision making. These exciting discoveries suggest this striatal region may also play a key role in the related process of sensory selection, wherein reward guides the relevant filtering of sensory inputs. Prefrontal inputs to disparate visual and auditory striatal regions within the tail have been shown to regulate multimodal sensory selection through inhibition of distinct sensory thalamic regions. Moreover, work in mouse somatosensory and visual systems have shown strong impacts of striatal dSPN activation on sensory-guided action. Additionally, recent work in rhesus monkeys suggests the indirect pathway is involved in the rejection of low-value visual targets. Together, this suggests the opponent basal ganglia

pathways in the tail function in task relevant auditory selection to ultimately shape goal-directed behavior. Specifically, we hypothesize dSPN recruitment in the tail is necessary for rewarded/target related responding whereas iSPN recruitment is necessary to inhibit unrewarded/distracted responding. To investigate this, we designed a lick based go/nogo behavioral paradigm where responses to distinct bandlimited sounds were either rewarded or punished with a timeout. Muscimol inactivation of the tail was able to reversibly impair behavioral performance, suggesting the tail of striatum may be required for the detection of task relevant auditory stimuli. Preliminary data from pathway specific optogenetic manipulations show converse contributions from SPNs in auditory-driven responding. Future directions aim to evaluate pathway specific neural activity in vivo to further investigate the opponent regulation of auditory filtering in the tail of striatum.

Disclosures: S.M. Ferrigno: None. **N. Zhang:** None. **M.V. Fuccillo:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.04/H10

Topic: E.03. Basal Ganglia

Support: NIH F31

Title: Exploring corticostriatal dynamics associated with auditory driven action impairments in Neurexin1 alpha mutant mice

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Abstract: Sensory processing impairments have been associated with a variety of neurodevelopmental disorders including autism spectrum disorder, Tourette syndrome, and attention-deficit/hyperactivity disorder, highlighting the need to understand its underlying neural mechanisms. Recent work has implicated basal ganglia's involvement in mediating sensory-driven action, with the tail of striatum being of particular interest as it receives heavy inputs from various sensory regions including auditory cortex. Moreover, prefrontal inputs to the tail of striatum are known to regulate multimodal sensory selection through inhibition of distinct sensory thalamic regions. Furthermore, direct stimulation of SPNs in the tail of striatum is sufficient to bias auditory discrimination. Taken together, these data suggest that disruption of corticostriatal inputs to the tail of striatum may contribute to some of the sensorimotor impairments commonly associated with these disorders.Copy number variation of genes encoding synaptic adhesion molecules, such as Neurexin1α (Nrxn1α), have been shown to confer a significantly increased risk for these neurodevelopmental disorders, however, the underlying neural dysfunctions associated with Nrxn1α loss remain to be fully understood. Recent findings in acute striatal slices have revealed that loss of Nrxn1α function results in decreased synaptic

strength of medial prefrontal cortical inputs to the indirect pathway of the dorsal striatum. However, it remains to be determined whether corticostriatal deficits to the tail of striatum drive aberrant sensorimotor function.To investigate sensory driven behavior and its underlying neural dynamics, we have developed a novel treadmill-based operant task for head-fixed mice which assesses responding to behaviorally relevant target sounds as well as behaviorally irrelevant distractors. Preliminary behavioral results suggest that mice with Nrxn1α mutation are more susceptible to distractor responding. Future experiments aim to describe the striatal population recruitment related to task performance in both Nrxn1α WT and Nrxn1α KO mice using in vivo and slice electrophysiological techniques. These findings will provide valuable insight into the neural pathology involved in neuropsychiatric and neurodevelopmental disorders while elucidating corticostriatal mechanisms involved in action control regulation.

Disclosures: N. Zhang: None. **S.M. Ferrigno:** None. **M.V. Fuccillo:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Topic: E.03. Basal Ganglia

Support: Hewitt Foundation Fellowship
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New Cornerstone Science Foundation

Title: Complementary Corticostriatal Circuits Orchestrate Action Sequencing

Authors: *B. ZHANG[1,2], C. GEDDES[2], X. JIN[1,3];
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Abstract: Action sequencing is fundamental to organized behavior. Critical decision at every moment to repeat current action or switch to a new one is essential for animal survival and reproduction. Dysfunctional action sequencing observed in various neurological and psychiatric conditions, such as Huntington's disease (HD), Obsessive-compulsive disorder (OCD), and Autism spectrum disorder (ASD), manifests as issues with repetitive behaviors and impaired switching. Despite the fundamental importance of this problem in action control, the neural mechanisms underlying action sequencing remain largely elusive. Moreover, the malfunctioning of these mechanisms in different disease conditions, which is crucial for developing therapeutic interventions, is not well understood. In this study, we employed a heterogenous action sequence task, the LLRR task, which encompasses both action repetition and switching. Through pharmacological inactivation, in vivo electrophysiology, optogenetic manipulation and slice

recording, we identified two corticostriatal pathways responsible for action repetition and switching. Under disease condition, we observed that the function of the switching pathway was altered, resulting in OCD-liked behavior. These results have important implications for understanding how the brain controls action repetition and switching in health and disease.

Disclosures: B. Zhang: None. **C. Geddes:** None. **X. Jin:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Program #/Poster #: PSTR463.06/H12

Topic: E.03. Basal Ganglia

Support: X.J. is a New Cornerstone Investigator

Title: A computational model of closed-loop cortico-basal ganglia circuitry unravels the neuronal mechanisms for sequence learning and execution

Authors: *Z. WANG[1], P. ZHANG[1], X. JIN[2,3];
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Abstract: Understanding the neural mechanisms underlying action sequence learning andexecution is crucial for explaining complex behaviors across species. The cortico-basalganglia-thalamo-cortical circuitry is known to play a critical role in the learning andexecution of action sequences, yet the specific synaptic and neuronal mechanismsremain largely unresolved. Here, we constructed a computational model of cortico-basal ganglia circuitry based on realistic neuronal anatomy. The model comprisesdistinct neuronal populations in the cortex (CX), striatal direct (dSPN) and indirect(iSPN) pathways, globus pallidus externus (GPe), subthalamic nucleus (STN),substantia nigra pars reticulata (SNr), substantia nigra pars compacta (SNc), andthalamus (Th), which connect to form a closed-loop cortico-basal ganglia-thalamo-cortical circuitry reflecting known anatomy. A dopamine-dependent reinforcementlearning mechanism is employed to adjust the synaptic weights of corticostriatalprojections. We found that the differential plasticity of synaptic weights between corticalneurons and distinct striatal neuronal subpopulations, arising from reinforcementlearning, can lead to the crystallization of specific action sequences such as left-left-right-right (LLRR) or right-right-left-left (RRLL). In the cortico-basal ganglia modelnetwork that learned to perform LLRR or RRLL action sequences, detailed analyseswere conducted to unveil the synaptic and neuronal mechanisms underlying sequenceinitiation, between-subsequence switching, and sequence termination. Furthermore,optogenetic stimulation of striatal dSPN facilitates ongoing action, while excitation ofiSPN causes action switching in the network model, consistent with animalexperimental results. These findings underscore the importance of the closed-loopcortico-

basal ganglia circuitry in sequence learning, and reveal the specific pathwaymechanisms governing action sequence execution. Through deep interaction andintegration with animal experiments, the model provides invaluable insights into thesynaptic and neuronal mechanisms underlying action sequencing in health anddisease.

Disclosures: Z. Wang: None. **P. Zhang:** None. **X. Jin:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR463.07/H13

Topic: E.03. Basal Ganglia

Support: New Cornerstone Investigator

Title: Dopamine dynamics in the Macaque Striatum During Saccade Sequences

Authors: *X. YAN[1], X. JIN[2,3];
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Abstract: Action sequencing is essential for the daily functions of animals, as nearly all learned or innate animal behaviors involve a series of action sequences. Previous research has identified the basal ganglia as the primary brain region responsible for learning and executing these sequences. Dysfunctions in the midbrain dopamine system, which lead to impairments in the basal ganglia, are primarily associated with movement disorders like Parkinson's disease. This condition manifests as bradykinesia, resting tremor and rigidity in affected individuals. The mechanisms through which dopamine regulates action sequence performance remain poorly understood. Consequently, our objective is to investigate the dynamics of dopamine within the basal ganglia, specifically focusing on the caudate putamen, and to identify the dopamine's roles in the initiation, termination, switching, maintenance of actions and reward prediction. We take advantage of the non-human primate model that is capable of learning and executing multiple combinations of sequences. Two rhesus macaques were trained to perform eight saccade sequences consisting of four movements of identical duration but varying in the combinations of directional elements (either left or right saccades), including LLLL, RRRR, LLRR, RRLL, LRLR, RLRL, LRRL, and RLLR. These sequences served as a behavioral foundation for identifying the neural correlates of action start, stop, switch, as well as for action monitoring and reward prediction errors. AAV viruses encoding the GRAB-DA dopamine sensor were injected into various locations covering both the caudate and putamen in the macaque brain. During experiments, we monitored dopamine dynamics using acute fiber photometry as the monkey performed the eight saccade sequences in random order. This design allowed us to analyze the differential dopamine signaling cross the sequence, subsequence and element levels. Our

findings indicate that dopamine dynamics not only drive action sequencing but also signal the reward value when the monkey behaves towards reward delivery.

Disclosures: X. Yan: None. **X. Jin:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Topic: E.03. Basal Ganglia

Support: Novo Nordisk Foundation Laureate Program (NNF15OC0014186)
Lundbeck Foundation (R345-2020-1769)

Title: Basal ganglia output control of caudal PPN

Authors: *G. SITZIA[1], J. CREGG[2,4], O. KIEHN[3];
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Abstract: Locomotion is a basic motor behavior required in most contexts of life, and its seamless execution depends on coordinated activity across multiple brain regions. The locomotor commands of start, speed, stop, and turn are executed by populations of excitatory brainstem neurons, under the control of upstream regions including the basal ganglia (BG). The glutamatergic neurons of the caudal pedunculopontine nucleus (Vglut2-cPPN) are essential for the start and speed of exploratory, goal-directed locomotion. We previously reported that Vglut2-cPPN neurons receive prominent inputs from basal ganglia (BG) output neurons, including the subthalamic nucleus (STN) and substantia nigra pars reticulata. Here we sought to establish the functional role of these diverse pathways with an initial focus on the cPPN-projecting neuronal subpopulation of the mouse STN. We used a retrograde viral approach to drive the expression of the excitatory opsin hChR2 in cPPN-projecting, Vglut2-positive STN neurons. Unilateral optogenetic activation of cPPN-projecting STN neurons is sufficient to elicit forward locomotion. The STN is a target for deep brain stimulation in Parkinson's Disease (PD). We performed injections of the dopamine D2 receptor antagonist haloperidol to induce an acute PD-like hypokinetic state. Optogenetic stimulation of cPPN-projecting STN neurons reliably brings the mice out of their akinetic state and promotes forward symmetric locomotion in Parkinsonian mice. In summary, cPPN-projecting neurons are a locomotor-promoting subpopulation of the STN, which might be a suitable target for alleviating locomotor dysfunctions in PD. In ongoing work, we are investigating the anatomical organization of cPPN-projecting STN neurons.

Disclosures: G. Sitzia: None. **O. Kiehn:** None.

Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Program #/Poster #: PSTR463.09/H15

Topic: E.03. Basal Ganglia

Title: Basal Ganglia pathways for regulating motor skill variability

Authors: S. ELVIG[1], O. OLADUNNI[2], ***S. WOLFF**[3];
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Abstract: Motor skills underlie much of what we do, from tying shoes to serving a volleyball. A hallmark of skills is a transition over learning, from variable behavior to precise and stereotyped movements. This change in motor variability must be flexibly, but tightly, regulated: while necessary to explore the motor space to find rewarded solutions, it impairs peak performance. However, how variability regulation is implemented in the mammalian brain remains unclear. The basal ganglia have been implicated, and a transition from dorsomedial striatum (DMS), mediating variable behavior, to dorsolateral striatum (DLS), driving stereotyped movement patterns, correlates with the variability decrease during learning. We suggest a novel mechanism which contributes to regulation of the DMS-DLS transition and thereby variability during skill learning and execution. The subthalamic nucleus (STN), an indirect pathway node, sends largely unexplored feedback connections to striatum: directly to DLS and indirectly to DMS via the anterior thalamic nuclei (ATN). STN receives broad cortical and subcortical input, allowing an integration of striatal signals with internal and external state information. Based on this, STN may modulate the DMS-DLS transition, thereby dynamically regulating motor variability. Indeed, chronic silencing of the STN-DLS projection impairs, while silencing of the STN-ATN or ATN-DMS projections promotes development of stereotypy and skill learning. Consistent with a DMS-DLS shift, STN-ATN silencing in experts has no effect, while STN-DLS silencing impairs stereotypy. Our results suggest novel roles for STN in regulating motor variability, likely by modulating DMS-DLS interplay, as well as unappreciated complexity in the basal ganglia circuitry.

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Poster

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Topic: E.03. Basal Ganglia

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Title: Striatal Control of Action Selection

Authors: *B. YANG[1], T. H. KIM[2], M. MARTIN[3], B. O. AHANONU[4], K. E. LANZA[5], X. WU[6], S. FLEPS[1], J. G. PARKER[7];
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Abstract: Executing appropriate behavioral responses to stimuli in the environment is essential to the survival of all species. In vertebrates, the basal ganglia are crucial for learning stimulus-motor responses. Specifically, dopamine release is thought to promote movement by activating direct pathway spiny-projection neurons (dSPNs) and inhibiting indirect pathway neurons (iSPNs) in the striatum. However, *in vivo* recordings showing that dSPNs and iSPNs co-activate in spatially overlapped clusters during spontaneous movement challenge this basic model. These results suggest that iSPNs constrain, rather than suppress movement, but they fail to explain dopamine's modulatory role in how the striatum encodes learned movement. Here we performed *in vivo* two-photon imaging of GCaMP Ca^{2+} activity in dSPNs and iSPNs simultaneously while the mice were trained in an active avoidance behavior task. We found that the dynamics with which dSPNs and iSPNs encode movement differed over the course of learning. To understand these differences, we are currently analyzing simultaneous recordings of dopamine transmission and dSPN or iSPN activity in mice learning the same task. Our results suggest that although dSPNs and iSPNs are simultaneously activated during motion onset, dopamine release may differentially modulate these dynamic to promote stimulus-response motor learning.

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Poster

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Program #/Poster #: PSTR463.11/H17

Topic: E.03. Basal Ganglia

Support: The Simons Collaboration on the Global Brain

Title: Dissection of inter-area interactions of motor circuits

Authors: *E. GJONI[1], **R. SRISTI**[2], H. LIU[1], S. DROR[2], X. LIN[1], K. M. O'NEIL[1], O. M. ARROYO, Jr.[1], S. HONG[1], S. BLUMENSTOCK[1], B. LIM[1], G. MISHNE[2,3], T. KOMIYAMA[1,3]; [1]Dept. of Neurobiology, Ctr. for Neural Circuits and Behavior, Dept. of Neurosciences, [2]Dept. of Electrical and Computer Engin., [3]Halicioğlu Data Sci. Inst., Univ. of California San Diego, La Jolla, CA

Abstract: Motor behaviors arise from dynamic interactions of interconnected neural populations across distributed brain areas. The underlying principles of information flow remain largely unknown. Here, we investigate the functional roles of motor cortex and intralaminar thalamus in driving specific cell populations of the striatum - the input nucleus of the basal ganglia - during movements. We recorded the activity of direct and indirect pathway medium spiny neurons (dMSNs and iMSNs) in the striatum as mice performed a skilled motor task, by in vivo two-photon calcium imaging through a GRIN lens. Furthermore, using monosynaptic pseudo-typed rabies virus we identified and imaged the activity of corticostriatal and thalamostriatal neurons that specifically project to dMSNs and iMSNs. We found that MSN population activity rises right after movement start, remains sustained throughout movement duration and peaks at the end of it. Contrasting dynamics characterizes their cortical and thalamic inputs, with corticostriatal activity concentrated around movement onset and offset and thalamostriatal activity engaged during movement execution. To explore differences among dMSNs and iMSNs and their inputs, we developed Trial Ensemble Attention network (TEA-net) - a recurrent neural network with attention that classifies neurons based on ensembles of their single-trial activity. This approach followed by clustering analysis revealed that MSNs are composed of heterogeneous functional subpopulations, some of which are cell-type specific. dMSNs and iMSNs were predominant in clusters with activity around movement onset/offset and in clusters with activity during movement, respectively. Cortical and thalamic neurons projecting to dMSNs and iMSNs showed activity patterns less distinct from each other, although they exhibited some functional subpopulations substantially composed by those targeting one striatal cell-type or the other. Preliminary experiments that combine striatal activity imaging with optogenetic manipulation of the inputs suggest that the contribution of cortical and thalamic inputs to MSN activity is dynamic during the motor task and specific to the targeted cell-type. The findings provide insights on the contributions of diverse long-range inputs to MSN subpopulation activity.

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Poster

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CONAHCyT Grant FDC_1702

Title: Exploring the contribution of the external segment of the globus pallidus to motor timing

Authors: *M. G. MARTÍNEZ-MONTALVO[1], D. I. ORTEGA-ROMERO[2], P. GONZALEZ-PEREYRA[2], C. I. PEREZ-DIAZ[3], P. E. RUEDA-OROZCO[4];
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Abstract: Exploring the contribution of the external segment of the globus pallidus to motor timing
Authors*M.G. Martínez-Montalvo, D.I. Ortega-Romero, P. González-Pereyra, C.I. Pérez-Díaz and P.E. Rueda-Orozco.Departamento de Neurobiología del Desarrollo y Neurofisiología. Instituto de Neurobiología, UNAM.
DisclosuresM.G. Martínez-Montalvo: None. **D.I. Ortega-Romero:** None. **P. González-Pereyra:** None. **C.I. Pérez-Diaz:** None. **P.E. Rueda-Orozco:** None.
AbstractThe basal ganglia (BG) are a group of subcortical structures related to movement and time perception. Previous studies manipulating the indirect pathway of the BG suggest its involvement in temporal processing, a possibility that has not been completely clarified. The external globus pallidus (GPe) is the first relay of the indirect pathway of the BG, which may be engaged in temporal processing during movement execution, a possibility that has not been clarified. The objective of this project is to evaluate the participation of the GPe, the first rely of the indirect pathway, in temporal processing associated to the execution of motor sequences. To this aim, we implemented two behavioral paradigms in rodents (mice and rats) and performed optogenetic manipulations and electrophysiological recordings during the task execution. In the first task, overtrained rats executed stereotyped movement sequences in a spatiotemporal context spanning hundreds of centimeters in seven seconds, while running on a motorized treadmill moving at random speeds. Our results indicate that optogenetic activation and inactivation of GPe produced longer and shorter movement sequences, respectively. Interestingly, these manipulations did not affect the animal's running speed or their adjustments to unpredictable changes of the treadmill speed. In the second task, head-fixed mice learned to move a lever with their left forepaw, producing two movement durations (200 ms and 500 ms) in alternating 20 trial blocks. Then, GPe high density electrophysiological recordings during this task execution revealed a pattern of sequential activity that begins hundreds of milliseconds before of movements start, followed by sustained inhibition while the lever movement is holding and, finally, another sequential activation after the reward delivery. The first two components of population activity showed a rescaling according to movement duration. Taken together, our preliminary results support the involvement of GPe neural activity in motor timing.

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Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Title: Segregated populations of neurons in the substantia nigra pars reticulata scale kinematic representations across different behavioral contexts

Authors: *A. S. BÁEZ-CORDERO[1], D. I. ORTEGA-ROMERO[2], A. HIDALGO-BALBUENA[2], C. I. PEREZ-DIAZ[2], P. E. RUEDA-OROZCO[2];
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Abstract: Movement execution requires coordinated activity between sensory and motor systems and involves several cortical and subcortical regions, including the basal ganglia (BG). While the specific mechanisms by which the BG influence movements remain unclear, previous reports have shown robust kinematic and contextual representations in their input (striatum) and output nuclei (susbtantia nigra pars reticulata, SNr). Hence, an attractive hypothesis is the BG implication in the control and adaptation of movement kinematics to different behavioral contexts. Here, we explore this possibility by using high-density electrophysiological recordings in freely moving rats and analyzing the neural activity of the SNr. Additionally, we explored if the functional identity of SNr neurons could be linked to their principal anatomical targets in the motor thalamus and the mesencephalic locomotor region. Recordings were performed during movement execution in two behavioral protocols with a different range of spatial and temporal content. In the first protocol, animals were required to perform locomotion runs constrained to a spatiotemporal range of meters and about 7 seconds. In the second protocol, the same animals were required to perform forelimb movements constrained to 3 to 10 centimeters in the order of hundreds of milliseconds. We found that the SNr spiking activity in both tasks was linearly correlated with kinematic parameters such as position and velocity, and these representations were adjusted to the different spatiotemporal scales of the movement. That is, the minimum and maximum SNr firing rates adjusted proportionally to the minimum and maximum ranges of speed/position on each task. Then, we asked if the same neurons would encode the same variables in both behavioral contexts. Recordings where the same neurons were recorded in both tasks revealed two subpopulations, one that maintained and one that changed their functional identites (i.e. speed or position modulated activity). Ongoing pathway-specific optogenetic manipulations combined with anesthetized and freely moving recordings will clarify if these segregated populations target different thalamic or mesencephalic regions. Our data suggest that while position and velocity signals are preserved throughout the BG, they scale and exhibit a different functional identity in a context-dependent manner, supporting their implication in the abstract representation of movement kinematic control.

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Poster

PSTR463: Basal Ganglia: Systems Behavior II

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Topic: E.03. Basal Ganglia

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Title: Striatal modular organization confirms direct pathway canonical role in movement control

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Abstract: The canonical role attributed to the direct/indirect pathways of the basal ganglia (BG) has been recently challenged, but new findings suggest that one source of discrepancy may be the anatomical organization of the striatum. We explored this possibility by stimulating direct pathway neurons (dMSNs) in distinct anatomical regions of the antero-posterior and dorsal-ventral axis of the sensorimotor striatum in different behavioral contexts. Our results indicate that in rats and mice, discrete striatal portions associated with somatotopic representations are also related to the promotion of specific behavioral patterns. For example, stimulating dMSNs in the hindlimb region in the dorsolateral striatum (hlDLS) reliably induced a stereotypical pattern of backward locomotion. This pattern was not related to stressful conditions and was independent of learning processes. On the other hand, stimulating dMSNs in the ventral striatal region produced stereotypical orofacial movements, without affecting locomotion patterns. These stereotypical patterns interfered with behavioral control under different experimental conditions and contexts, giving the impression of behavioral arrests. For example, forward locomotion was slowed down or even cancelled when stimulating hlDLS but not anterior or ventral regions of the striatum. Our results support the direct pathway canonical role related to movement promotion but reveal the existence of a striatal modular organization where the simultaneous activation of different modules may result in behavioral arrests, potentially conciliating previous discrepancies.

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Poster

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Topic: E.03. Basal Ganglia

Title: Neuronal dynamics of pedunculopontine GABAergic neurons during action sequence initiationand execution

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Abstract: The pedunculopontine nucleus (PPN) is a midbrain structure that is part of the mesencephalic locomotor region. Emerging data suggest the involvement of PPN neurons in the modulation of goal-directed behavior and the consolidation of stimulus-outcome associations. These functions may be attributed to its bidirectional connectivity with multiple basal ganglia nuclei, including the dopamine neurons of the substantia nigra. We have recently reported that PPN_{GABA} neurons inhibit dopamine neurons and modulate goal-directed responses of unsigned valence, affecting the completion of tasks that entail both appetitive and aversive outcomes without interfering with the overall motor output. However, it is not clear whether PPN_{GABA} neurons signal the termination of a goal-directed action sequence (i.e., facilitating a switch in behavior when contingencies change), or whether they participate in shaping the execution of goal-directed behavior (i.e., tracking the progression of an action sequence). Here, we explored the group dynamics of PPN_{GABA} neurons during different stages of goal-directed behavior using fiber photometry. We transduced PPN_{GABA} neurons with a calcium indicator (GCamp) in VGat-Cre mice and we trained them in a lever-pressing task. Photometry recordings were obtained following the completion of a fixed ratio (FR) paradigm with progressive increases of the sequence length (i.e., FR1, FR3 and FR5). In the following stage of the experiment, mice were tested in a progressive ratio paradigm to record the activity of PPN neurons around the breaking point (i.e., termination of the sequence determined by the mice). We observed that PPN_{GABA} neurons increased their activity at the start of every lever-pressing sequence (FR1, FR3, FR5 and PR). Following the initial peak of fluorescence, corresponding to the first lever press, the activity decreased but remained higher than the baseline during the entire sequence. During the head entry to the reward port, the activity of PPN_{GABA} neurons increased again before returning to baseline levels. Unpurposive movement was not correlated with changes in calcium signaling. Our results support the theory that PPN_{GABA} neurons track the entire action sequence and possibly contribute to its initiation and termination. Further experiments will test the possibility of functionally different subtypes of PPN_{GABA} neurons based on their projection targets.

Disclosures: S. Zhang: None.

Poster

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Topic: E.03. Basal Ganglia

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Title: Segregated striatal populations represent the distinct actions organized into skilled sequences

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Abstract: Skilled behaviors are composed of sequences of actions requiring a precise in order to achieve a specific goal. Extensive work has implicated the basal ganglia as playing a crucial role in the learning and execution of skilled behaviors. The neural mechanisms in the basal ganglia that mediate the coordination of the action components remain unclear. In this study, we recorded extracellular spiking activity of medium spiny neurons (n = 1512) in the dorsal (DLS) and ventral (VLS) striatum while freely-moving mice (n = 7) perform a forelimb reaching task for drops of sucrose. Using high-speed video analyses, we identified three actions with distinct kinematic profiles that are sequenced to produce the reaching behavior: aiming for the water target, reaching with the forelimb, and drinking from the hand once the water is acquired. Distinct populations of MSNs in the striatum represent kinematics associated with either the aiming, reaching, and drinking components of the behavior. These representations show a rough spatial topography. If a given action was being performed the corresponding action-related population is active, while the other populations are inactive. During learning, initial attempts to reach the water with the tongue are rapidly suppressed as reaching becomes gradually inserted into the proper action sequence. Following learning, the licking behavior, primarily mediated by VLS neurons, is only initiated upon the completion of the reach and the placement of the paw close to the mouth. Optogenetic stimulation of direct pathway neurons in the VLS targeting the licking-related populations resulted in persistent generation of the licking action directed at the water target, and akinesia of the paw for the duration of stimulation. Together these findings reveal that distinct action components are represented by distinct neuronal populations in the striatum. During skill learning, there is a development of a selective inhibition mechanisms whereby competing actions are suppressed at specific points in the sequence.

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Poster

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Support: CRCNS

Title: Geometry of neural representations underlying unconstrained, naturalistic behavior

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Abstract: To make movement and foraging decisions in a naturalistic environment, motor cortex and striatum must work synergistically to produce successful actions. These decisions span multiple scales, from kinematic control of vigor, to broader decision motifs associated with a given context. We simultaneously recorded from neurons across these areas as a mouse freely explored an open-field. We then applied our unsupervised behavioral clustering tool, B-SOiD, to identify distinct movements, behaviors, and action motifs from animal pose and aligned to behavioral onset. Significant patterns of co-activation across neurons in these areas enables the responses of single cells to be well-explained by a small set of underlying 'latent' dimensions. Here we establish the multi-scale geometry responsible for encoding the range of representations underlying spontaneous, naturalistic behavior.
Traditional methods of explaining shared variability in neural populations often involve linear tools (e.g. PCA, GPFA) applied to neural data collected during artificial, overtrained tasks; however, we have shown that the naturalistic behaviors of mice in the open field require an appreciation of more complex dimensionality. Recent approaches utilize nonlinear dimensionality reduction methods to produce more succinct descriptions of comodulation—i.e. learning latent dimensions nonlinearly related to recorded neural firing rates. How populations of striatal and cortical neurons covary in naturalistic settings absent overtraining and rigid restrictions on movement has yet to be evaluated. In this unconstrained naturalistic foraging, we find that motor cortex lacks complexity. Activity patterns can be equivalently described by nonlinear and linear methods across a range of diverse representations. In striatum, however, a nonlinear mapping more compactly captures activity both when applied to individual behaviors and composite actions, providing evidence for a complex latent dependency between striatal neurons which is independent of motor output or behavior. We find that these shared activity patterns shift over the course of a four-hour session in both striatum and M1. These results raise further questions about the structure of naturalistic behavior representation and the coordinated translation of this information between areas.

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Poster

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Title: Developmental and adult striatal patterning of nociceptin ligand marks striosomal population with direct dopamine projections

Authors: *E. HUESKE[1,2], C. STINE[3], T. YOSHIDA[4], J. CRITTENDEN[4], J. LOFTUS[4], A. GUPTA[1], J. JOHNSON[3], A. ACHANTA[3], A. MAHAR[4], D. HU[4], J. AZOCAR[4], R. GRAY[1], M. R. BRUCHAS[3], A. M. GRAYBIEL[4];
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Abstract: Circuit influences on the midbrain dopamine system are crucial to adaptive behavior and cognition. Recent developments in the study of neuropeptide systems have enabled high-resolution investigations of the intersection of neuromodulatory signals with basal ganglia circuitry, identifying the nociceptin/orphanin FQ (N/OFQ) endogenous opioid peptide system as a prospective regulator of striatal dopamine signaling. Using a prepronociceptin-Cre reporter mouse line, we characterized highly selective striosomal patterning of *Pnoc* mRNA expression in mouse dorsal striatum, reflecting early developmental expression of *Pnoc*. In the ventral striatum, *Pnoc* expression was clustered across the nucleus accumbens core and medial shell, including in adult striatum. We found that $Pnoc^{tdTomato}$ reporter cells largely comprise a population of dopamine receptor D1 (*Drd1*) expressing medium spiny projection neurons localized in dorsal striosomes, known to be unique among striatal projections neurons for their direct innervation of midbrain dopamine neurons. These findings provide new understanding of the intersection of the N/OFQ system among basal ganglia circuits with particular implications for developmental regulation or wiring of striato-nigral circuits.

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Poster

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Support: Army Research Office W911NF-16-1-0474
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Title: Cost-benefit decision-making and learning in primates: exploring the interconnected roles of orbitofrontal and anterior cingulate circuits

Authors: *G. K. PAPAGEORGIOU[1], D. J. GIBSON[2], K.-I. AMEMORI[4], H. SCHWERDT[5], M. WANG[6], V. MCMILLAN[1], J. SHARMA[3], U. UPADHYAY[7], A. M. GRAYBIEL[1]; [2]McGovern/BCS, [3]Brain and Cognitive Sci., [1]MIT, Cambridge, MA; [4]Inst. for the Advanced Study of Human Biol. (ASHBi), Kyoto Univ., Kyoto, Japan; [5]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [6]Univ. of Toronto, Toronto, ON, Canada; [7]Neurosurg., Boston Univ. Sch. of Med., Boston, MA

Abstract: The prevalence and diagnosis of mood-related disorders have seen a strong rise in recent decades. While our grasp of the pathophysiologic aspects has improved, a comprehensive understanding of the brain structures and circuits involved remains elusive. In our research with non-human primates, we focused on two critical areas within the corticostriatal pathway: the pregenual anterior cingulate cortex (pACC) and the caudal orbitofrontal cortex (cOFC). The pACC is known to play roles in learning, decision-making, and mood regulation. By contrast, the cOFC, located in the posterior part of the orbitofrontal cortex, has not been as extensively studied; research has predominantly concentrated on the medial and lateral regions of the OFC. To deepen our understanding of these neural circuits, we trained two adult macaque monkeys, one male and one female, in a task that involves visual cues for approach and avoidance decisions (Ap-Av task). This task, which has been used in previous studies involving both non-human and human subjects, required the monkeys to make choices about accepting or rejecting offers that presented a mix of rewards and punishments. We monitored the monkey's brain activity using both chronic platinum iridium probes and acute S-probes during task performance. Alongside electrophysiological data, we also monitored physiological metrics such as pupil diameter, lick rates, and pulsimetry to assess the behavioral state of the subjects. Once both monkeys had become proficient at the task and showed consistent behavior, electrical microstimulation (EMS) was applied on separate occasions using either high (150-200 μA) or low (5-15 μA) current intensities. The analysis of the electrophysiological recordings during the learning phase indicated that neural units in both the pACC and cOFC responded to most of the task's events. Notably, the cOFC exhibited greater overall activity compared to the pACC, except during adverse outcomes where the pACC appeared more active. Further examination showed that the pACC tended to be inhibited during the cue period, in contrast to the cOFC, which displayed a more balanced level of activity during the same period. Physiological data analysis also highlighted a strong correlation with the monkeys' behavioral responses. Sessions with EMS, delivering either high or low currents at precisely targeted sites within these regions, led to an increase in avoidance behaviors, wherein the monkeys predominantly rejected offers. These findings underscore the critical roles of the pACC and cOFC in cost-benefit decision-making and their direct influence on mood regulation.

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Poster

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Title: Representation of Rhythmic Chunking in Striatum of Mice Executing Complex Continuous Movement Sequences

Authors: *K. HIROKANE[1], Y. KUBOTA[2], D. HU[1], T. YAGI[3], A. M. GRAYBIEL[1], T. KITSUKAWA[4];
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Abstract: Many of our actions, such as playing musical instruments or engaging in sports, involve continuous coordinated movements among multiple body parts. This coordination demands precise timing and positioning of body parts, presenting a challenging problem known as “combinatorial explosion” due to the enormous number of possible combinations of joint angles, muscle contractions, and other parameters.In our previous work, we demonstrated that motor chunking occurs during complex movement execution using a ‘step-wheel’—a motor-driven, Ferris wheel-like device allowing mice to adapt their locomotion patterns to the configuration of pegs serving as footholds. We observed that mice formed a motor chunk that the interval and phase were solidified. We suggested this as a potential mechanism for reducing computational demands, a concept we refer to as the ‘*rhythmic chunking hypothesis*.' Our latest study expanded on our previous work by recording spike activity from the dorsolateral striatum of mice running on the step-wheel. We observed a highly patterned activity of striatal medium spiny projection neurons (MSNs), which was closely linked to the chunking behavior observed during the task. These MSNs responded not only to specific intervals and phases between both forelimb gait cycles, but also to the repetition number of a specific interval-phase stepping pattern. We propose here the formation of 'chunking fields' in striatum, akin to hippocampal

place fields but encoding temporal movement pattern rather than spatial pattern. Interestingly, in contrast to our observations in the striatum, we did not find neurons in the neocortex that responded to a combination of all chunking parameters. However, we did identify many cortical units that fired in relation to individual chunking parameters, with only a few responding to multiple parameters. This suggests that in the neocortex, interval, phase, and repetition could be encoded as separate events, whereas in the striatum, these parameters are integrated to form chunking fields. We found further that the coordination of completely different body parts using rhythmic chunking could be mediated by the striatum, as we found the neurons tuned to licking and locomotion coordination. Our findings could be critical for understanding movement disorders such as Parkinson's disease. We posit that the diminution or loss of such encoding capacity could relate to the gait disturbance and loss of rhythm notable in Parkinson's disease as the dopamine input to the striatum becomes reduced over time. Our study calls for examination of the relationship between dopamine release in the striatum and this MSN activity.

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Poster

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Title: Striosomes target nigral dopamine-containing neurons via direct-D1 and indirect-D2 pathways paralleling classic direct-indirect basal ganglia systems

Authors: *I. LAZARIDIS[1], J. R. CRITTENDEN[1], G. AHN[1], K. HIROKANE[1], T. YOSHIDA[1], V. SKARA[2], K. MELETIS[2], K. PARVATANENI[1], J. T. TING[3], E. A. HUESKE[1], A. MATSUSHIMA[1], A. M. GRAYBIEL[1];
[1]McGovern Inst. for Brain Res., MIT, CAMBRIDGE, MA; [2]Karolinska Inst., STOCKHOLM, Sweden; [3]Human Cell Types, Allen Inst. For Brain Sci., Seattle, WA

Abstract: The basal ganglia's classic output pathways, known as the direct-D1 and indirect-D2, or "Go/No-Go" pathways, are crucial for normal movement control, and their imbalance contributes to movement disorders such as Parkinson's disease. Here, we introduce a parallel system of direct-D1 and indirect-D2 pathways originating from the striosome, rather than the matrix, compartment of the striatum, targeting dopamine neurons in the substantia nigra pars

compacta (SNpc) rather than the basal ganglia's motor output nuclei. Our findings demonstrate that the direct striosomal D1 pathway and a novel, distinct indirect striosomal D2 pathway modulate striatal dopamine release and respond differently during task performance and to stimuli, depending on their striatal positions. This striking parallelism between striosomal and matrix pathways necessitates a reevaluation of the traditional basal ganglia model, suggesting these circuits not only modulate action but also motivation, influenced by their connections to limbic and cortical inputs. Our proposed model underscores a potentially new therapeutic target within these pathways, particularly the D2 pathway, affected by many existing drugs. This comprehensive framework aligns two circuit sets with shared organizational principles but distinct outcomes on movement and motivational processes.

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Poster

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Title: Dynamics of dopamine release in substantia nigra in Pavlovian and instrumental learning

Authors: *A. MATSUSHIMA, K. TRAN, D. HU, T. YOSHIDA, J. LOFTUS, A. M. GRAYBIEL;
MIT, Cambridge, MA

Abstract: The release of dopamine (DA) in the striatum has been widely studied due to the innovation of dopamine sensors. However, dopamine release in the substantia nigra (SN) has not been characterized so far *in vivo*, save in single fast-scan cyclic voltammetry (FSCV) human study (Batten et al., 2024). Thus, its intra-nigral function remains elusive. A hint comes from a previous study on slowly developing Parkinson's disease (PD) mouse model (González-Rodríguez et al., 2021), which demonstrated that the loss of nigral dopamine release measured *in vitro*, rather than loss of striatal dopamine release, emerged with the deficits in gross sequential movement as a proxy of 'freezing gate'. We applied GRAB-DA3h *in* vivo to the SN in head-fixed mice and recorded nigral DA signaling as they acquired Pavlovian and instrumental tasks.Pavlovian task: A conditional visual cue was presented, followed by liquid reward delivery. The recorded nigral DA release signals were tightly correlated with licking, but the patterns of modulation differed depending on mouse, and in some cases, on the stage of acquisition. When

we aligned to the onset and offset of licking bouts, DA signaling rose significantly preceding lick bout onsets and fell as a trend, preceding the bout offsets; the modulation was larger for longer bouts, suggesting that the nigral DA release reflects the vigor to initiate and continue licking.Instrumental breakpoint task: Mice were rewarded for licks, but the number of licks required increased exponentially. Thus, the more the mice licked, the more reward they received up to the point at which they gave up (break point, the cost-benefit equation). To factor out modulation by motor activities, we fitted a liner regression model and predicted DA release from the licking activities, and subtracted these from the original data. The nigral DA release was higher before the successful completion of high efforts trials, in which more licks were required and executed to obtain a reward, than before low effort trials. After reward delivery, nigral DA release also was higher after larger efforts were expended. This pattern was observed across mice and could not be replicated solely by the linear regression model of licking activity. *Thus, dopamine release signaling in SN reflects not only the licking movements but also the effort expended or to be expended*.These results open a new way to understand the functions of the nigro-striato-nigral loop and its role in motor and psychiatric disorders.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Title: Ventral-dorsal stream interactions supporting functional object grasps

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Abstract: Visual cues drive inferences necessary for everyday object-directed actions. For instance, when grasping a hammer to pound a nail, one grasps its handle off of its center of mass, rather than at its midpoint. How are visual cues integrated with a representation of the goal of an object-directed action in order to constrain where and how to grasp the object? This study tested the role of interactions between the ventral and dorsal visual pathways in translating visual cues into functionally appropriate object-directed actions. In Study 1, participants were shown a pair of 3D novel objects on every trial during fMRI scanning; the pair was either the same or

different in surface texture (rough/smooth), shape (same shape or isomer), or material property (made of metal, wood, or stone). Consistent with prior findings, we found a strong preference for material properties in ventral occipitotemporal areas. In Study 2, participants viewed small familiar manipulable objects and were asked to identify the object's center of mass. Our findings demonstrated that participants showed differential neural activity in the collateral sulcus and anterior intraparietal sulcus (aIPS) when computing the balance point for manipulable objects. These studies support the view that interactions between the collateral sulcus and aIPS support the integration of surface visual cues of objects into functionally appropriate object directed grasps.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Title: Two distinct networks for encoding goals and forms of action: an effective connectivity study.

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Abstract: Goal-directed actions are characterized by two main features: the content (i.e., the action goal) and the action vitality forms (VF) (i.e., how actions are executed). The processing of the action content is mediated by a brain network composed by a set of parietal and frontal areas. In contrast, the network encoding the action vitality forms (e.g., gentle or rude actions) has not yet been characterized. Previous fMRI studies showed that the observation and execution of actions endowed with VF activate, in addition to the parieto-frontal network, the dorso-central insula. In the present study, we established, using Dynamic Causal Modeling (DCM), the direction of information flow during observation and execution of actions endowed with gentle and rude VF in the human brain. Based on previous fMRI studies, for the DCM analysis we selected the following nodes: the posterior superior temporal sulcus (pSTS), the inferior parietal lobule (IPL), the premotor cortex (PM), and the dorso-central insula (DCI). Bayesian model comparison showed that, during action observation, two streams arose from pSTS: one towards IPL, concerning the action goal, and one towards DCI, concerning the action vitality forms. During action execution, two streams arose from PM: one towards IPL, concerning the action

goal and one towards DCI concerning action vitality forms. The modulation effect of PM on DCI opens a new important perspective regarding the execution of action VF. It suggests that VF could have a *cognitive* and an *affective* origin. When VF are cognitively planned, it might involve the activation of the frontal lobe and subsequently activate PM and then DCI. In this view, when the agent voluntary decides to perform an action VF, the parieto-frontal circuit modulates the DCI. In this way, the motor action acquires an affective component. In contrast, when vitality forms convey a real positive or negative affective state, they might originate in DCI and possibly, in some subcortical structures, and modulate the parieto-frontal circuit selecting the appropriate motor act encoded in PM area. Pooling together, our findings open a new question concerning the possibility to elicit VF in two distinct ways: cognitively (from PM to DCI) and affectively (from DCI to PM).

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Title: Cortical representation of formal control-theoretic algorithms for visuomotor control during active navigation

Authors: *T. ZHANG, C. STRONG, K. C. STOCKING, J. LI, C. TOMLIN, J. L. GALLANT; Univ. of California, Berkeley, Berkeley, CA

Abstract: Visuomotor control is crucial for navigating through naturalistic environments, as we must dynamically adjust our actions to account for the behavior of others. The intraparietal sulcus (IPS), motor cortex, supplementary motor areas (SMA), and the prefrontal cortex (PFC), have all been implicated in visuomotor control. However, it remains unclear what control algorithms these regions implement, and what control-related features they represent, during interactions with other agents. Here, we examined whether the brain uses algorithms similar to control theoretic models developed in the engineering community for car-following. We used fMRI to record brain activity from six participants performing a taxi-driver task in a large virtual world (110-180 minutes of data per participant). In this task, participants had to constantly monitor other vehicles and adjust their own actions. To discover whether the brain uses

algorithms similar to control theoretic models, we first implemented three control theoretic car-following models: the optimal velocity model (OVM) and intelligent driver model (IDM), two reactive dynamical systems models; and a model predictive control (MPC) model that integrates forward prediction with reactive dynamics. We tuned the parameters of these three control models to match the behavior of each participant, and used these participant-specific tuned models to create features for modeling brain activity. Next, we used banded ridge regression to estimate voxelwise encoding models for these control models along with 34 other feature spaces for the taxi-driver task. Results show that the MPC encoding model explains much more variance in brain activity than can be explained by the IDM and OVM encoding models. Well-explained regions include the IPS, SMA, motor cortex, and parts of the PFC. Analysis of the MPC encoding model weights shows that each of these regions is tuned for different combinations of MPC features, and reveals that these regions are also temporally tuned across the MPC prediction horizon for each feature. These results suggest that, for optimal visuomotor control during driving, the human brain may recruit multiple cortical regions to implement a MPC-like forward predictive algorithm.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Topic: E.04. Voluntary Movements

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Title: Differentiating neural substrates related to phonological working memory and motor programming in speech sequence learning

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Abstract: Speech sequencing is the process of transforming a linguistic message into a sequence of articulatory gestures. To facilitate fluent speech, frequently produced sequences are thought to be encoded as “chunks” to conserve neural resources, rather than being built from scratch each time. However, the precise nature of these chunks and the neural mechanisms underlying this process remain unclear. As speech sequencing encompasses multiple stages—phonological encoding, phonetic encoding, and motor execution—different neural mechanisms and chunk units may be used across these stages. To explore these differences, we previously designed a

syllable repetition task involving CCVCC stimuli (CC: consonant cluster; V: vowel) that violate English phonological constraints (e.g., *GBASF*). Task performance was assessed under three conditions: fully learned syllables ***[FL]***, partially learned syllables ***[PL]*** (where CCs were practiced as parts of other syllables), and novel syllables ***[N]***. Our prior studies with this paradigm noted similar shorter utterance durations in both the *FL* and *PL* conditions compared to the *N* condition (*N* > *PL* ≈ *FL*). However, error rates in the *PL* condition were lower than the *N* condition but higher than the *FL* condition (*N* > *PL* > *FL*). These findings suggest different neural mechanisms behind these two measures. In the current study, 15 monolingual American English speakers performed the illegal syllable repetition task during sparse sampling fMRI scans. We observed that brain regions associated with phonological working memory [PWM], such as the posterior inferior frontal sulcus and pre-supplementary motor area, exhibit a blood-oxygen-level-dependent (BOLD) response pattern of *N* > *PL* ≈ *FL*, mirroring the pattern seen in the behavioral results for utterance duration. In contrast, regions linked to motor programming (e.g., ventral premotor cortex) display a pattern of *N* > *PL* > *FL*, matching the pattern observed in the behavioral results for error rate. These findings are consistent with the interpretation that utterance duration is most affected by PWM processes, whereas articulatory error rate is predominantly influenced by motor programming processes, given the minimal working memory demands of producing a single syllable. We also confirmed that brain areas thought to be purely motoric (i.e., without regard for phonological processing), including the supplementary motor area and ventral motor cortex, show no significant differences in activity across conditions. Together, these findings offer important empirical evidence for refining neural models of the motor speech sequencing process.

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Poster

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Title: Pragmatic representation of self and other's action in the monkey putamen

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Abstract: The basal ganglia are involved in a variety of motor functions, from action selection and movement initiation to postural regulations. Anatomical data in monkeys demonstrated that areas of the cortical Action Observation Network, involved in the encoding of executed and observed manual actions, send convergent projections to overlapping territories of the putamen nucleus. Recent findings have suggested that the cortical coding of other's action plays a crucial role in regulating social interactions, but the potential contribution of the basal ganglia to self and other's action coding and its pragmatic relevance in social interactions remains unknown. Here, we addressed this issue by recording neuronal activity of 573 neurons with linear multielectrode probes from histologically verified regions of the motor putamen in two monkeys during a Mutual Action Task. In this task, the monkey and an experimenter, facing the same device in a shared space in between them, took turns based on contextual cues to grasp - or observe the other agent grasping - the same multi-affordance object with a precision grip or with a whole hand prehension. We found action-related neurons (*n = 245*) encoding selectively monkeys' own action (*Self-type, ST; n = 157*), the other agent's action (*Other-type, OT; n = 32*), or both (*Self-and-other type, SOT; n = 56*). Object selectivity emerged in 24% of neurons responding to executed action, but almost exclusively after movement initiation, suggesting its corticostriatal origin, whereas action observation responses lacked object/grip specificity. Furthermore, differently from cortical territories of putaminal projections, the monkey's hand visual feedback during object grasping did not modulate putaminal neurons. Interestingly, when other's trials occurred in the dark, OT and SOT neurons did not reduce their response, suggesting a role of these cells in inhibiting movement onset during partner's action. In line with this hypothesis, we found that the interposition of a transparent barrier between the target object and the monkey during experimenter's trials resulted in an overall decrease of neuronal activity, supporting a pragmatic function of putamen neurons in gating action execution while observing others in social contexts.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Title: Frontoparietal cortical activity during a combined approach of action observation and proprioceptive stimulation reveals long-term plasticity in primary motor cortex

Authors: *M. BOVE[1], A. BISIO[1], M. BIGGIO[1], C. IESTER[1], S. BRIGADOI[2], S. CUTINI[2], L. BONZANO[1];
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Abstract: Combining action observation (AO) and proprioceptive stimulation (PS) evokes a kinaesthetic illusion (KI) of movement and increases the excitability of the primary motor cortex (M1) up to one hour after the end of its administration. Although M1 excitability during the stimulation is an individual marker of plasticity, other cortical areas might determine the consequences of AO-PS. Furthermore, previous AO-PS protocols were based on repeated stimulations aimed at evoking KI. However, KI is subjective and characterized by a large inter-individual variability. Finding a protocol that succeeds in evoking plasticity while being unconstrained to the individual KI would lead to more robust results. In this work, we assessed the changes in cortical hemodynamic activity by means of functional near infrared spectroscopy during the administration of a new AO-PS protocol, not evoking KI, and we tested its ability in inducing M1 plasticity in 21 healthy participants. AO-PS was composed of 50 bursts of combined stimuli. Each burst consisted in 5 couples of AO-PS, each one lasting 1s, interleaved by 1 s-pause, for a total duration of 10 s. Each burst was separated from the next by a pause of 10-13 s. During each AO-PS couple, participants observed a video showing thumb abduction towards the palm and simultaneously received a mechanical vibration of the extensor pollicis brevis muscle (stim. freq.: 80 Hz). Recruitment curves (RC) were measured by means of transcranial magnetic stimulation before, immediately, 30 min and 60 min after AO-PS, to evaluate changes in M1 excitability. During AO-PS administration, the optodes were arranged resulting in a total of 44 standard channels (3 cm) and 8 short-separation channels (8 mm), covering a frontoparietal cortical network. RC were compared at the different evaluation epochs to test the occurrence of M1 plasticity. Results showed a significant increase of M1 excitability 30 min after AO-PS, suggesting the possibility for this new AO-PS protocol to evoke plasticity in M1. During AO-PS, a significant increase in oxy-hemoglobin concentration was found in a frontoparietal network, including the following Brodmann's areas (BA): right and left BA1, 2, 3, left BA4 and BA6, right and left BA40 and right BA44. The amount of plasticity evoked in M1 by AO-PS significantly correlated with the activity of prefrontal brain regions involved in the control of voluntary movement and in attentional mechanisms. These results show that the proposed AO-PS protocol can induce long-term increase of M1 excitability regardless of the necessity to evoke an illusory sensation of movements and point to the role of frontoparietal network in evoking this phenomenon.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Program #/Poster #: PSTR464.07/H34

Topic: E.04. Voluntary Movements

Title: Movement duration modulates the readiness potential

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Abstract: The readiness potential (RP) is a slow negative shift in cortical activity that precedes voluntary movement and reflects processes involved in movement preparation and planning. While the RP has been extensively studied in relation to various aspects of motor control, the effect of movement duration on RP parameters remains largely unexplored. This study aimed to investigate how the duration of a voluntary movement modulates the onset, duration, and amplitude of the RP.Twenty-four healthy, right-handed male university students were divided into two groups and performed two series of 30 repetitions of a voluntary right elbow flexion task. The movement durations were set at 2 and 6 seconds for each series. EEG was recorded from the parieto-frontal circuit, specifically at the Pz, Cz, and F3 electrode sites. Results showed that RP duration was significantly longer for movements lasting 6 seconds compared to those lasting 2 seconds. This finding was consistent across both groups and all analyzed electrodes. Interestingly, movement duration did not modify RP onset or amplitude. These findings suggest that the RP is related not only to the onset of movement but also to its duration, with longer duration movements requiring more prolonged cortical activation in the parieto-frontal circuit. The extended cortical activation time observed for longer movements may be attributed to the increased complexity of controlling movements of extended duration. Longer movements likely require more sustained motor planning and execution, leading to a prolonged RP. Importantly, in this study, RP duration was measured from RP onset to RP offset, rather than from RP onset to movement onset as traditionally done. This novel approach to quantifying RP duration implies that the RP reflects the entire movement execution process, not just its initiation.The findings of this study have potential implications for motor learning and control. Longer duration or slower movements may be more effective for the process of motor learning and control, as they allow for more extended cortical activation and potentially more time for sensory feedback integration and error correction. In conclusion, this study demonstrates that movement duration modulates the readiness potential, specifically its duration, highlighting the importance of considering movement duration in the study of motor preparation and control. Future research should further investigate the mechanisms underlying this modulation and its potential applications in motor learning and rehabilitation.

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Poster

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Program #/Poster #: PSTR464.08/H35

Topic: E.04. Voluntary Movements

Title: Excitability and plasticity of the motor cortex across the menstrual cycle

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Abstract: Concentrations of ovarian hormones fluctuate across the eumenorrheic menstrual cycle, which contribute to modulations in cortical excitability and inhibition. Oestrogens have an excitatory effect, whilst progesterone has an inhibitory effect within the motor pathway. However, it is unknown how such changes affect nervous system adaptation (neuroplasticity), which has the potential to improve functional capacity in health and disease. The aim of this study was to determine the effect of the menstrual cycle on motor cortical excitability and plasticity. Data is presented for ten of the seventeen female participants who have completed testing so far (age 26 ± 6 years). Participants reported a regular menstrual cycle (≥21 & ≤35 days) and no hormonal contraceptive use over the previous 6 months. After familiarisation, participants visited the lab in three phases of the menstrual cycle: early follicular (EF), late follicular (LF), and mid luteal (ML). One menstrual cycle was tracked with calendar counting and urine ovulation testing prior to data collection, which was repeated with additional blood samples to confirm hormone concentrations during the tested cycle(s). During each visit, participants received transcranial magnetic stimulation (TMS) and percutaneous nerve stimulation at baseline to quantify corticospinal excitability (MEP), short-intracortical inhibition (SICI), intracortical facilitation (ICF), and sarcolemmal excitability (Mmax). This was followed by a paired associative stimulation (PAS) protocol of median nerve (300% perceptual threshold) and TMS (120% resting motor threshold [rMT], 25 ms interstimulus interval, 200 pairs at 0.25 Hz) to assess neuroplasticity. Baseline assessments were repeated immediately, 15, and 30 minutes after the PAS protocol. rMT (50 ± 12, 51 ± 13, 50 ± 11 %MSO) and MEP amplitude (7.5 ± 6.2, 7.5 ± 4.8, 7.9 ± 4.4 %Mmax) remained consistent across phases, for EF, LF and ML, respectively. SICI induced inhibition (43.0 ± 27.9, 47.2 ± 21.9, 45.0 ± 31.4 %unconditioned MEP) and ICF induced facilitation in all phases (168.1 ± 64.5, 149.3 ± 53.5, 160.1 ± 57.6 %unconditioned MEP). PAS elicited an increase in excitability in the EF (146 ± 58%, $p = 0.035$) and LF phases (136 ± 27%, $p = 0.009$), but not the ML phase (114 ± 29%, $p = 0.167$). Given the incomplete sample size at present, phase effects from ANOVAs were not detected for any variables ($p > 0.262$). While caution should be taken interpreting this incomplete sample, it appears that PAS elicited neuroplasticity may be blunted in the ML phase, suggestive of an inhibitory effect of progesterone, which has implications for functional capacity in health and disease.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Title: Human corticospinal input-output modulation and the influence of GABA during action preparation: A TMS and MRS study

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Abstract: Preparing a motor action changes the input-output properties of the corticospinal (CS) pathway. Multiplicative neural computations of input-output properties, referred to as gain modulation, depend on inhibitory gamma-aminobutyric (GABA)-ergic mechanisms in sensory cortices, but the role of GABA in the primary motor cortex (M1) is less clear. This study aimed to investigate the relationship between CS gain modulation during action preparation and intrinsic GABA availability in M1 using transcranial magnetic stimulation (TMS) and magnetic resonance spectroscopy (MRS). We hypothesized that CS input-output gain would change in a preparation-dependent manner and that stronger modulators would have greater M1 GABA capacity. Human participants (n = 31) performed instructed-delay two-choice reaction time tasks. Single-pulse TMS was used to derive modulation of CS input-output to the left hand when it was task-relevant and task-irrelevant during action preparation. We used nonlinear mixed effects modeling to evaluate interindividual differences in CS input-output modulation between task-relevant and task-irrelevant contexts, normalized to a pre-response baseline. MRS was used to measure water-referenced and tissue-corrected GABA concentrations in left and right M1 as well as a control occipital lobe voxel. Context-dependent modulation of CS input-output was explained by group-level additive ($F_{3,578} = 16.1$, $P < 0.001$) and multiplicative ($F_{3,578} = 29.6$, $P < 0.001$) changes. MRS analyses using Bayesian correlations indicated GABA concentration was positively correlated between left and right M1 ($r = 0.32$, $BF_{10} = 1.91$) but not between left or right M1 and the occipital lobe ($BF_{10} < 0.3$). However, preliminary analyses showed no relationship between the CS input-output gain modulation and GABA in either M1 or the occipital lobe (all $BF_{10} < 1$). These results have several implications for our understanding of the neuronal processes underlying goal-directed action preparation. First, our data indicate canonical computations well-described in sensory cortices generalize to the human motor system. Moreover, our findings align with computational models of the motor cortex that indicate a specific role of gain modulation in action preparation. Lastly, interindividual differences in CS input-output may not be explained by differences in intrinsic GABA availability across the primary motor cortices.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Topic: E.04. Voluntary Movements

Support: University of Georgia Mary Frances Early College of Education and University of Georgia Office of Research

Title: Goal-dependent modulation of corticospinal excitability during perception of moving targets

Authors: *J. R. MCCURDY, K. ARIGA, E. WHITMAN, D. A. BARANY;
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Abstract: When intercepting moving targets, humans move their eyes both to estimate target speed and to guide hand movements. Projections from multiple brain regions important for eye movements, motion perception, and motor planning converge on human primary motor cortex (M1), but how visual and motor information is integrated in M1 to facilitate accurate perception and interception is unclear. Here, we applied single-pulse transcranial magnetic stimulation (TMS) over M1 while participants judged the time of arrival for a moving target to investigate the influence of eye movements and movement preparation on human corticospinal excitability. On each trial, a target would appear and approach a fixed interception zone at one of two constant velocities. Participants (N = 11, 4M, 21.3 ± 2.7 years) were instructed to either intercept the oncoming target when it was within the interception zone or to only view the target's motion without intercepting. On all trials, participants were asked to judge whether the target's velocity was faster or slower than a reference target that appeared immediately following each trial. Across blocks of trials, participants were instructed to track the target using smooth pursuit eye movements or fixate on the interception zone. Motor-evoked potentials (MEPs) in response to M1 TMS were elicited from the right first dorsal interosseus muscle at baseline, 200 ms after the onset of target motion, or at one of two latencies (300 ms, 150 ms) relative to the target's arrival at the interception zone. We observed that movement times were shorter (F (1,10) = 7.87, p = 0.019) and interception accuracy improved (F (1,10) = 6.31, p = 0.031) when participants followed the target with smooth pursuit eye movements. The time course of corticospinal excitability depended on whether the goal was to intercept the target or to simply view it (F (1.1, 10.8) = 5.55, p = 0.037): on interception trials, MEPs were reduced relative to baseline at 200ms after target onset and at 300ms prior to target arrival and facilitated at 150 ms prior to arrival. In contrast, when participants were instructed to only perceive the target's motion, MEPs were reduced relative to baseline at all TMS timepoints. Altogether, these results indicate that

different types of eye movements influence interception performance, and that the preparatory modulation of corticospinal excitability depends on the behavioral goal.

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Poster

PSTR464: Action, Action Perception, and Complex Movements

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Topic: E.04. Voluntary Movements

Support: MNESYS - A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)

Title: Does the modality of haptic interaction affect the emergence of coordinated behavior?

Authors: L. BANDINI, C. DE VICARIIS, *V. SANGUINETI;
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Abstract: We often interact with other individuals and develop forms of coordinated actions. The Prisoner Dilemma game has been often used as a general model of how two agents develop mutual cooperation. Two prisoners, held in separate cells and unable to communicate, must decide whether to accuse the other (defect, d) or stay silent (cooperate, c). If both agents cooperate, they serve few years. If they both defect, they get more years. But if only one defects, he goes free and the other gets even more years. Defect-defect (dd) is the only Nash equilibrium (NE) when the game is played once, but iterated play enables a richer range of behaviors, including cooperation (cc). In a sensorimotor version of the game, the two agents interacted through a dyadic haptic interface and the game cost matrix was encoded into the stiffness of a virtual spring, whose magnitude depended on the movements of both players. Iterative play with this version of the game resulted in a robust convergence to NE. These differences may have different explanations. The two games may share the same cost structure but not the same NE. Haptic interaction encodes the action cost into movement effort, but potentially provides more information on partner actions. To understand the different outcomes of the two versions of the game, we designed a haptic scenario in which the overall movement cost was matched with the discrete cost matrix and the NEs were set to be identical in the two games. We manipulated the overall stiffness magnitude (low, high) and the amount of information about partner actions - the stiffness either depended on the initial position or varied continuously with the players' positions (fixed and variable feedback modality). A total of 20 dyads participated in this study (five dyads for each of the four conditions). The experimental protocol involved a total of 200 trials. For each dyad, we analyzed the probability to converge to one of the four possible scenarios (dd, cc, dc, cd) over the last 100 trials. We also analyzed the action time series by using a computational model that assumes that each agent selects the action minimizing its expected cost, given the predicted partner action. We found that the probability to converge to NE is significantly greater

in high-stiffness dyads, but no effect of feedback type. The model correctly captured the behavior of the dyads that converged to the NE, but not the significant fraction of dyads that exhibited different behaviors. Overall, these findings suggest that minimization of mechanical effort is very hard to reverse. Those dyads with poor NE convergence also exhibited poor model fitting, suggesting that their behavior could not be interpreted as merely cost-optimal.

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Poster

PSTR465: Motor Learning in Animals

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Program #/Poster #: PSTR465.01/H39

Topic: E.04. Voluntary Movements

Title: Beyond reward: unveiling dopamine's role in encoding effort prediction error for motor learning

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Abstract: To learn to perform movements optimally, the mathematical framework of optimal control requires both a signal that evaluates reward outcomes, and a signal that tracks effort expenditures. The current dopamine (DA) reward prediction error framework posits that DA influences movement selection indirectly by motivating movements towards rewarding outcomes. However, it doesn't fully explain the function of nigrostriatal DA neurons projecting to the motor striatum (dorsolateral striatum, DLS), particularly concerning DA's role in energizing motor output and invigorating movements. Recent evidence suggests that DA neurons, beyond their involvement in reward processing, may multiplex feature-specific error signals for different types of learning, highlighting a hypothesized role of dopamine in encoding prediction error signal within the motor domain.To ask whether DA encoded effort expenditure and played a role in learning optimal control, we developed a force-field motor adaptation paradigm for head-fixed mice. As the mice learned to compensate for the force-induced motor errors during reaching, we monitored DA circuit activities, focusing on both DA transients at axon terminals and somatic spiking. We found that the spatially dissociable dopaminergic pathways to the DLS and ventral striatum (VS) conveyed distinct signals related to expended physical effort and reward-related motivation. Specifically, the DLS-DA transients encoded a signed effort prediction error in proportion to the discrepancy between the actual exerted and predicted effort. In contrast, the VS-DA transients transmitted a generalized motivation signal necessary for task engagement. Furthermore, the trial-by-trial update in pre-action DLS-DA levels predicted the proactive steering efforts to counteract impending force perturbations. Our findings enhance current understanding of the nigrostriatal dopaminergic projections to the motor striatum, establishing a direct link between effort prediction error signalling with learning

optimal actions. Attributing an energizing function to dopamine provides a compelling explanation for the characteristic bradykinesia observed in Parkinson's disease. Disruptions in motor striatal DA signalling could lead to an overestimation of the physical effort required for movement, consequently reducing motor vigor towards slower, low amplitude movements.

Disclosures: Q. Li: None. **Q. Chevy:** None. **S. Ren:** None. **R. Shadmehr:** None. **A. Kepecs:** None.

Poster

PSTR465: Motor Learning in Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.02/H40

Topic: E.04. Voluntary Movements

Title: Cell-type-specific corticostriatal dynamics orchestrate trial and error motor learning

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Abstract: Here, we establish a multi-area, cell type identified blueprint for the updating and performance of skilled actions. The performance of skilled actions is not instinctual - rather, it is learned through trial and error. Despite its importance, we still do not possess a mechanistic understanding of how the multiple cell types and areas comprising the corticostriatal axis work together to facilitate this learning. We have proposed a functional model of motor performance in which pyramidal tract (PT) and intratelencephalic (IT) neurons of motor cortex (M1) dictate motor commands, while the direct and indirect spiny projection neurons (dSPN, iSPN respectively) of the dorsal striatum regulate the performance kinematics of those plans based upon performance history. Using new molecular approaches, we optogenetically identified and recorded simultaneously across these cell types of the corticostriatal axis while a mouse performed a goal directed reach-to-target task in which the target bounds would randomly change mid-session.
With this rich neurobehavioral dataset, we sought to determine how the neural population changed after manipulating the target and what task variables were driving their activity using regressive approaches. We found that after moving the target bounds, encoding of peak amplitude on the upcoming reach increased in dorsal striatum and Layer 5 of M1. The encoding of the kinematic parameter of amplitude peaked before the reach in IT neurons and during the reach for both dSPNs and iSPNs. We also found that all neurons were sensitive to trial outcome and in some cases this encoding was more robust than in ventral striatum, which was also recorded from in these experiments. Interestingly neurons that were sensitive to information pertaining to the previous trial were found first in Layer 2/3 of the motor cortex prior to reach initiation as well as in both PT and IT neurons at the start of the reach, supporting their involvement in a feedback loop involved in the modulation of actions following an error.

This work suggests that upon recognizing a change in task demands, the neural population first identifies and then orchestrates the appropriate update to motor performance and computations specific to an upcoming goal-directed reach are carried out in L2/3 and both PT and IT neurons of M1. In comparison, dSPNs, iSPNs and IT neurons are more sensitive to the kinematics of the reach during movement. The encoding of trial outcome however, is distributed across both cortex and striatum, but utilized at different times during and after the reach, pointing to a global feedback signal that can be used to update behavior in different ways.

Disclosures: M.A. Nicholas: None. **E.A. Yttri:** None.

Poster

PSTR465: Motor Learning in Animals

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Topic: E.04. Voluntary Movements

Support: Fellowship 749154 from CONAHCyT-México
UNAM-DGAPA-PAPIIT: IA201020, IN200822
CONAHCyT: FDC_1702, CF-2023-I-7

Title: Preconfigured cortico-thalamic neural dynamics constrain movement-associated thalamic activity

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Abstract: Neural preconfigured activity patterns (nPAPs) have been proposed as building blocks for cognitive and sensory processing. However, their existence and function in motor networks have not been explicitly studied. Here, we explore the possibility that nPAPs are present in the motor thalamus (VL/VM) and their potential contribution to motor-related activity. To this end, we developed a preparation where VL/VM multiunitary activity could be robustly recorded in mouse behavior evoked by primary motor cortex (M1) optogenetic stimulation and forelimb movements. VL/VM-evoked activity was organized as rigid stereotypical activity patterns at the single and population levels. These activity patterns were unable to dynamically adapt to different temporal architectures of M1 stimulation. Moreover, they were experience-independent and present in virtually all animals, confirming their preconfigured nature. Finally, subpopulations expressing specific M1-evoked patterns also displayed specific movement-related patterns. Our data demonstrate that the behaviorally related identity of specific neural subpopulations is tightly linked to nPAPs.

Disclosures: P. Gonzalez-Pereyra: None. **M.G. Martínez-Montalvo:** None. **D. Ortega:** None. **C.I. Perez-Diaz:** None. **H. Merchant:** None. **L.A. Tellez:** None. **P.E. Rueda-Orozco:** None.

Poster

PSTR465: Motor Learning in Animals

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Program #/Poster #: PSTR465.04/I2

Topic: E.05. Brain-Machine Interface

Support: Allen Institute
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HHMI

Title: Studying the role of cortical circuit plasticity during learning

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Abstract: Learning skills involves coordinated changes in neural activity in wide-spread neural circuits. It is often not clear if activity in a particular group of neurons is causally related to behavior. In contrast, Brain Computer Interface (BCI) learning allows the experimenter to define the mapping from activity to action, potentially simplifying the study of learning.
With the goal of identifying the synaptic and circuit mechanisms underlying learning, we developed a novel BCI behavioral task: mice control the position of a reward port using the activity of a single, 'conditioned neuron' (CN) in layer 2/3 of primary motor cortex, recorded with two-photon calcium imaging. At trial start the port is out of reach. Activity in the CN drives the approach of the port with a 10 s integration time.
During the first day of training, 10-20% of neurons become modulated after trial start, and these dynamics are stable across days. Each day, a new CN is chosen that has no obvious task-related activity. Mice improve the rate of rewarded trials from 50% to 75% within the first 25 trials (5 minutes), driven by an increase in CN activity. Learning is remarkably sparse: Less than 3% of imaged neurons increase their activity to the same degree as the CN. High-speed videography and bodypart tracking revealed small but significant learning-related changes in movements of specific body parts.
To probe changes in network connectivity, we used all-optical methods to measure the effective connections in the vicinity of the CN. Neurons whose task-modulated activity increased during

learning became connected to each other. To assess the causal involvement of local circuit plasticity, we perturbed the activity of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), an enzyme critical for induction of synaptic plasticity, using the light-activatable CaMKII inhibitor paAIP2. Preliminary results indicate that transient inactivation of CaMKII interferes with learning, implying that BCI learning in motor cortex requires local circuit plasticity and likely Ca^{2+}-dependent synaptic plasticity.

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Poster

PSTR465: Motor Learning in Animals

Location: MCP Hall A

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Program #/Poster #: PSTR465.05/I3

Topic: E.04. Voluntary Movements

Support: NSF GRFP
R01 NS094184

Title: Activity patterns of Parvalbumin-expressing interneurons during dexterous reach-to-grasp skill learning in mice

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Abstract: The ability to learn new behaviors is a critical aspect of brain function. While it has long been clear that Parvalbumin-expressing (PV) interneurons are important for stabilizing neural activity, recent work suggests that they also play a crucial role in learning (Chen et al., 2015) (Murray et al., 2015). PV neurons target the soma of excitatory cells (Buhl, et al., 1994) (Kepecs & Fishell, 2014), and because they are recurrently connected with excitatory cells and receive similar input, they have the potential to provide tight control of spiking activity (Safari et al, 2017). Moreover theoretical work suggests that PV neurons play an important role in stabilizing new groups of task-associated excitatory neurons (Bos et al., 2020) (Lagzi et al., 2021), which is consistent with experimental work showing that PV neurons regulate the size of engrams in the amygdala (Morrison et al., 2016). Here, we examine how correlations between PV neurons and excitatory neurons evolve during the emergence of novel task related neuronal subnetworks in a mouse motor skill learning paradigm. We use two photon imaging to longitudinally record dynamic calcium signals in all neuron types in caudal forelimb area of the mouse motor cortex over a minimum of 14 days, using a mouse model in which PV neurons express tdTomato. We train mice in a difficult dexterous task where they must reach for, grasp, and carry a pellet that is placed precariously on a pedestal. The task requires precise placement

of their digits to prevent the pellet from being knocked off, ensuring that the mice must carefully execute the task each time, even after they have learned it. This task has been shown to require intact motor cortex in mice for performance as well as acquisition (Guo et al., 2015). Because changes in PV activity have been reported very early in learning (Donato, et al., 2013), we record neural activity beginning in the earliest stage of learning when the mice are first presented with pellets, commonly referred to as the shaping phase. We construct functional networks using pairwise correlations between neurons, including between PV neurons and excitatory neurons, and measure how functional networks change over task learning. This enables us to measure task related subnetworks of excitatory neurons and explain how the relationship between PV neurons and neurons in task-related subnetworks changes throughout the learning process. By employing network science tools to develop functional networks from evolving pairwise correlations, we effectively analyze and explain the dynamic interactions between excitatory and PV neurons within task-related subnetworks as they change during the learning process.

Disclosures: G. Wheeler Fox: None. **E. Wiener:** None. **J.N. MacLean:** None.

Poster

PSTR465: Motor Learning in Animals

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Simons Collaboration on the Global Brain Pilot Award

Title: Causal role of motor cortex dynamics in a learned movement revealed by targeted holographic stimulation

Authors: *Q. CHEN[1,2,3,4], A. WU[1,2,3,4], B. YU[1,2,3,4,5], Z. TAN[1,2,3,4], T. KOMIYAMA[1,2,3,4,6]; [2]Neurobio., [3]Neurosciences, [4]Ctr. for Neural Circuits and Behavior, [5]Electrical and Computer Engin., [6]Halıcıoğlu Data Sci. Inst., [1]UC San Diego, La Jolla, CA

Abstract: The primary motor cortex (M1) is essential for motor learning and movement execution. Learning a novel motor skill induces a reproducible neural activity pattern in the layer 2/3 (L2/3) of M1. Nevertheless, it is unclear whether this learned activity pattern causally instructs the learned movement. To address this question, we leveraged *in vivo* two-photon calcium imaging combined with holographic optogenetic stimulation to stimulate specific ensembles of M1 L2/3 neurons in mice skilled at a lever-pressing task. We found that stimulating ~20 neurons whose activity onset in voluntary trials precedes movement onset can induce

movements that resemble the learned movement. Examination of neural activity revealed that the optogenetic stimulation triggered activity patterns in other neurons not directly stimulated that resemble the population activity patterns underlying voluntary movements. Trial-by-trial variability of optogenetically triggered population activity patterns predicted the induced movement kinematics, similarly to voluntary movements. Furthermore, the initial state of population activity patterns immediately preceding optogenetic stimulation was predictive of the triggered movement kinematics on a trial-to-trial basis. Stimulation of the same number of other neurons failed to induce the learned movement. Taken together, we conclude that the activity pattern in M1 L2/3 causally instructs learned movements, and both the initial state of the network and precise inputs are necessary for this function.

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Poster

PSTR465: Motor Learning in Animals

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Topic: E.04. Voluntary Movements

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Title: Role of medial prefrontal cortex in long-term learning of motor skills

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Abstract: Long-term skill learning refers to the practice-dependent process of acquiring new motor skills from an initial fragile to a more consolidated stage, with improved speed and accuracy. Notably, skill learning has been often characterized by having a fast phase (typically associated with rapid gains in performance) and a slow phase (associated with changes in speed-accuracy and slow refinement of the level of skill). Our recent work has suggested that the mPFC plays a role in the transition from early learning to the slower phase of late learning. Here, we were specifically interested in uncovering the causal role of mPFC in long-term skill learning as well as determining how mPFC neural dynamics evolve over time. To test the potential causal relationship between mPFC and behavioral stabilization, we lesioned mPFC prior to the onset of learning. Interestingly, the mice were able to demonstrate improvements in performance during the early phase (typically < 5 days). However, in the absence of mPFC, there were no further long-term gains in comparison to control animals. Similar results were observed with the application of optogenetic or chemogenetic manipulations in mPFC. Together, this indicated that mPFC has an essential role in driving the transition from fast to slow learning. We then

monitored mPFC neural activity using a miniscope while the mice learned the reach-to-grasp task. We found evidence for the gradual emergence of sequential mPFC neural dynamics that spanned long-time scales, preceding the onset of trial start cues tothe end of trial as well as covering the following intertrial period. The time scale of crystallization of such long-duration dynamics, which appeared to predict the upcoming task start cue and the behavioral outcomes, was closely matched to the transition from fast to slow learning. We interpret the emergence of such a long timescale sequential pattern as important for 'understanding' the task goal and for predicting the following task outcomes; both of these are likely to be important for the slow refinement of long-term motor skill acquisition. Together, our results suggest the casual importance of mPFC in the transition from fast learning to a slower phase of refinement that is essential for long-term motor skill learning.

Disclosures: L. He: None. **Z. Wang:** None. **K. Ganguly:** None.

Poster

PSTR465: Motor Learning in Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR465.08/I6

Topic: E.04. Voluntary Movements

Title: Point cloud registration reveals systematic changes in cortical population activity during motor learning

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Abstract: Previous studies have explored the changes in spatial tuning of single neurons in the motor cortices during learning, finding heterogeneous changes among neurons, and generating conflicting theories with respect to the neurons' relation to movement kinematics or kinetics, and the presence or absence of a sustained "memory" component. Here, we view the activity across a full population of neurons as a point in a low-dimensional state space. Over many trials, the neural activity forms a point cloud with structure that may change across time and experimental conditions. To investigate the effects of learning on these point-cloud representations, we applied point cloud registration, an approach used in computer vision, to the activity of neurons in the primary motor (M1) and dorsal premotor (PMd) cortices of monkeys learning to reach in a curl force field. We trained a deep neural network to learn either a rigid or a non-rigid transformation from the neural point cloud during the baseline period before learning to that after the monkey had learned the curl field. We characterized the geometric form of the learned transformation as a combination of shifting, scaling and rotation. We examined whether the varied responses of individual neurons could together induce a recognizable transformation in population activity. In general, 3D M1 point clouds had good target separation and could be accurately transformed by a rigid rotation and scaling, with the rotation direction opposite that of the force field. More

poorly-learned targets were not as well fit by such rigid transformations, but a nonrigid typically worked. Intriguingly, the required rotation from adaptation to washout was approximately the inverse of the initial rotation. Together, these findings suggest that the altered tunings of individual neurons in M1 collectively resulted in a systematic transformation at the population level during learning; they do not, however, support the existence of a sustained "memory" component accompanying the changes in neural activity. Unlike M1, PMd point clouds in 3D showed less target separation for both preparation (prior to the go cue) and movement phases; only a nonrigid transformation served to align the point clouds before and after learning that only moderately well compared to M1. However, for 8D PMd point clouds, the target separation was clearer and an accurate rigid rotation could be identified. Our findings suggest more complex population changes in PMd, perhaps due to the interacting effects of preparation and execution during learning. We plan to explore these differences, and their relation to limb mechanics in subsequent studies.

Disclosures: X. Ma: None. **Q. Xian:** None. **L.E. Miller:** None.

Poster

PSTR465: Motor Learning in Animals

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Program #/Poster #: PSTR465.09/I7

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant
Scottish Rite Charitable Foundation of Canada Award

Title: Motor learning deficits in a mouse model of Fragile X Syndrome

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Abstract: Fragile X Syndrome (FXS) is the most prevalent inherited intellectual disability and the most common monogenic cause of autism spectrum disorder (ASD). It causes an array of deficits including impaired motor learning and coordination, which are essential skills for daily life and survival. Despite its impact on quality of life, how different parameters of movement learning evolve during skill acquisition, and the underlying neural circuit mechanisms, remain incompletely understood. To investigate this, we trained C57BL/6 wild-type (WT) mice and a Fragile X Syndrome mouse model (*Fmr1* KO) of both sexes to perform a single-pellet skilled forelimb reaching task. Our results show that *Fmr1* KO mice have a learning deficit, achieving significantly lower success rates by the end of training than WT mice. In order to understand the differences in movement learning that underlie the deficit in success rate, precise measurement

and analysis of the reaching movements across training is required. Therefore, to measure reach trajectory and kinematics, we automated the task with a motorized door cue synchronized with high-speed video recordings to track their movements using DeepLabCut. Remarkably, we found that overall, *Fmr1* KO mice significantly learned and achieved success rates similar to WT mice in the forelimb reaching task when the automated door cue was present. This suggests that the learning deficit can be alleviated with the right cues to aid learning. Detailed movement analysis revealed refinement of reach trajectories in both WT and *Fmr1* KO mice with the automated door, aligning with a significant increase in success rate in both groups after training. Notably, despite achieving comparable success rates, modulation of reach trajectories during learning is different between WT and *Fmr1* KO mice. This could suggest the possibility that the *Fmr1* KO mice developed alternate strategies to achieve success, or that the observed difference in reach trajectory modulation is not sufficient to impact success rate. The improvement in learning we observed in response to the door cue raises the question of what causes it at the cellular and circuit level. These experiments reveal a previously undescribed behavioral phenomenon and highlight the importance of future work to elucidate the underlying mechanisms using in vivo measurements of neural activity during learning. Understanding the neural differences underlying the learning deficit can help us build the foundational knowledge needed to aid the development of targeted treatments for FXS and similar conditions.

Disclosures: L. Young: None. **A. Suvrathan:** None.

Poster

PSTR465: Motor Learning in Animals

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Topic: E.04. Voluntary Movements

Support: NIH R01 EY024067

Title: Primate motor cortical spindles reflect sleep-dependent consolidation of sequence learning

Authors: *D. BAKALOV[1], A. L. ORSBORN[3], K. KUMAR[4], S. QIAO[5], K. WINGEL[2], C.-H. CHIANG[6], C. WANG[6], J. VIVENTI[6], B. PESARAN[2];
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Abstract: Sequential movements, like typing, are vital for daily functions. Motor sequence learning, assessed through sequential motor tasks, is consolidated during overnight sleep, particularly during non-rapid eye movement (NREM) sleep. Sleep spindles, bursts of 11-16 Hz activity, are involved in consolidating these procedural memories. The motor cortex is thought to play a key role in this consolidation, yet studies have been limited. In rodents, single unit recordings link skill acquisition rates with replay of task-related neural activity during NREM

sleep, specifically coinciding with spindle bursts. Compared to rodents, non-human primates (NHPs) are a more translational model organism, sharing similar sleep patterns and motor cortical topography with humans. However, technical challenges of recording cortical activity in NHPs during naturalistic 8-hour sleep cycles have limited studies examining sleep dynamics. We studied sequence learning in two adult male Rhesus monkeys (*Macaca mulatta*) using a center-out reaching task with a predictable sequence over several days. Motor sequence learning was assessed by the rate each monkey correctly acquired sequence targets before their presentation. Both monkeys showed significant improvement in task performance within and across the first five days of learning. We implanted a microdrive that recorded simultaneously (0.1 - 10 kHz) from up to 32 microelectrodes within the motor cortex and 62 micro-electrocorticographic (μECoG) electrodes on the surface, spaced 200μm apart. Wireless recordings captured motor cortex activity during naturalistic sleep in a cage instrumented with video tracking. We identified periods of sleep using overnight video recordings that were aligned to the corresponding μECoG data, which was then used to label 10-second increments of spectral activity as REM or NREM sleep. Spindles were detected by band-pass filtering the microelectrode data between 11-16 Hz and identifying instances when the signal envelope exceeded 2 standard deviations above the mean for 0.5-3 seconds. During NREM sleep, both monkeys showed significant differences in spindle rates across microelectrodes over the first five days of learning. The Kruskal-Wallis test indicated significant differences for Monkey J ($H = 15.25$, $df = 4$, $p = 0.004217$) and Monkey G ($H = 19$, $df = 4$, $p = 0.000787$), with the highest spindle rates in the first 2-3 days. These findings suggest spindle-driven consolidation in the NHP motor cortex during sequential movement acquisition. Further analysis will examine spindles across μECoG contacts to assess spatial and temporal correlations with microelectrode spindles.

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Poster

PSTR465: Motor Learning in Animals

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Topic: E.04. Voluntary Movements

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Title: Motor adaptation in high-dimensional input spaces occurs through a combination of model-driven feedforward control and sensory-driven feedback control

Authors: *K. M. PERKS[1], L. I. SMITH[2], S. A. BURDEN[2], A. L. ORSBORN[2,3,4];
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Abstract: Introduction: To control a familiar motor effector, like a computer mouse, we rely on both sensory information from the environment (feedback control) and internal models about the way the effector works (feedforward control). But how do we adapt to unfamiliar effectors that we might not have internal models of? Human psychophysics studies have identified multiple types of motor adaptation by exposing users to visuomotor perturbations, which alter the visual feedback associated with movements. However, these experiments often use manipulations (e.g. error clamping) to study only adaptation in model-driven feedforward control. They also use simplified tasks where the dimensionality of user movements (input space) matches that of visual feedback (output space), which does not reflect the redundancy of real-life effectors. We aimed to simultaneously study feedforward and feedback control changes during high-dimensional motor learning. Our novel approach combines perturbations in a rich input space with a task that disentangles feedforward from feedback control (Yamagami et al., 2021; Yang et al., 2021). **Methods:** We first trained two male rhesus macaques to control the movement of a 1D cursor using unconstrained 3D hand movements. We specified an 'intuitive' initial control axis in 3D space M_i onto which hand position was projected and transformed into cursor position. The monkeys used M_i to perform a continuous tracking task, which consisted of following a pseudo-random moving target while also correcting for a disturbance applied to the cursor. The target and disturbance trajectories contain distinct frequencies, which enable separate quantification of feedforward and feedback control. Once the monkeys were well-trained on the task using M_i, we leveraged the higher-dimensional input space to create perturbed control axes M_p (N=8), which rotated M_i by 20°, 60°, 90° or 180°. As the monkeys adapted to the perturbations, we recorded their movements and quantified their feedforward and feedback control to link changes in each type of control to changes in behavior and performance. **Results:** The monkeys adapted to all M_p, with larger rotations requiring more practice to achieve M_i performance levels. For each M_p, they developed a strategy of moving along a 'compromise' axis that split M_i and M_p. In line with this, we found the monkeys did not always learn good internal models of M_p. Surprisingly, modulating feedback control contributed just as much to performance gains as internal model updates. Our results provide novel insight into how motor adaptation occurs in previously unstudied contexts and will enable new ways to study the neural mechanisms of motor learning.

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Poster

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Title: Adapting a turntable task paradigm to study neural circuit dynamics underlying grasping in the intact and injured primate brain

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Abstract: Rhesus monkeys have an exceptional ability to plan, reach, grasp and manipulate objects to achieve behavioral goals. These behaviors are thought to involve multiple brain areas such as the motor, premotor, and parietal cortices. However, we currently do not understand the coordinated in-vivo neural circuit dynamics across layers of these brain areas that underlie mechanisms of grasping, and how these laminar dynamics are altered by cortical injury. Answering these questions necessitates 1) a rich behavioral paradigm to elicit complex reaching and grasping of a variety of shapes and 2) measurement of arm and finger kinematics during the behavior. We were inspired by recent efforts (Buchwald et al, 2021, Frontiers in Behavioral Neuroscience) and adapted this design. Our experimental workspace for the macaque monkey is composed of a turntable with slots for six different objects that can vary in size, shape, and weight, as well as cue LEDs to indicate to the animal the planning and movement epochs. The front of the workspace has a light curtain that can be used to detect premature reaches into the workspace and thus withhold reward or stop the motion of the turntable if the monkey attempts to reach while it is in motion. Finally, to detect when and whether the object has been lifted, we use a retroreflective photoelectric sensor that has a beam that is blocked when the object is down but visible when the object is lifted. For reach to grasp assessment, we used a FLIR camera to capture the arm reach and the fingers grasping the object and used Deeplabcut and video scoring to estimate hand kinematics.
We trained one monkey (Y) to reach and grasp objects in the turntable and measured reaction times for six different objects. In a typical session, monkey Y can perform ~400 trials of a delayed reach to grasp task. We found that reaction times (RTs) in this task were related to the size, shape, and novelty of the shape, with the longest RTs and lowest reach accuracy for objects that were novel or more difficult to pick up due to shape or weight. Qualitative analysis of these hand trajectories also suggested that objects could elicit a range of grasp postures and finger configurations.
Future work will use multiple cameras for use with Anipose to estimate 3D trajectories of the hand. Ongoing experiments aim to leverage this rich behavior and Neuropixels recordings to study the laminar microcircuit dynamics in dorsal premotor cortex, ventral premotor cortex, and motor cortex that drive grasping. We anticipate using this turntable design and our established lesioning approach to understand the neural circuit dynamics underlying recovery from motor cortical injury.

Disclosures: N. Carr: None. **T. Wang:** None. **R. Sinha:** None. **J. Salamy:** None. **T.L. Moore:** None. **C. Chandrasekaran:** None.

Poster

PSTR465: Motor Learning in Animals

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Program #/Poster #: PSTR465.13/I11

Topic: E.04. Voluntary Movements

Support: Brain Canada Foundation
CIHR

Title: A computer vision platform unveils cortical neural correlates of spatial reaching in rats

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Abstract: The rat model serves as a fundamental tool for fundamental research investigating neuronal control of movement and its adaptation after neurotrauma. A classic paradigm to evaluate changes in fine motor skills in rats is the single pellet reaching and grasping task. Most studies employing this task rely only on gross measurements of reaching and grasping such as whole task success/fail, or in some cases a more detailed but time-consuming visual expert scoring of motor execution. An environment specifically tailored for fine kinematic evaluation of hand movements in rats has lacked, and this has limited the scientific power of characterizing of neuronal functions involved in controlling hand and arm movements in the rat model.
This study presents a novel platform, based on single pellet reaching and grasping in the three-dimensional space in front of rats. Using computer vision from a 60 frames per second (fps) real-time video stream, the pellet positioning of the task was automatized. We demonstrate real-time camera-based scoring, which can be used for automated task training protocols. The evaluation of this online animal performance exhibits an error rate of 3.4%, with all errors stemming from conditions that do not impact a task difficulty progression. Four additional high-speed cameras record hand movements at 200 fps during reach attempts. The synchronized video streams are processed by a pose estimation pipeline composed of the DeepLabCut and Anipose algorithms, for precise three-dimensional tracking of forelimb kinematics.
We further obtained primary motor cortex recordings from two female Long Evans rats, equipped with 32-channel cortical implants through an open source bioamplification module (Open Ephys) sampling at a frequency of 30 kHz to track neuronal activity during 3D reaching. Diverse neural activity profiles, encompassing various patterns and phase preferences, reveal phase-dependent modulation of cortical activity during reach and grasp movements. Our platform allows us to associate neural trajectories with 3D task kinematics. It can enable novel studies on neuronal function in 3D skilled movement in rodents.

Disclosures: E. Theberge: None. **K. Parker:** None. **R. Picard:** None. **J. Zhao:** None. **S. Quessy:** None. **N. Dancause:** None. **M. Bonizzato:** Other; Cofounder of 12576830 Canada Inc., a startup company working on cortical stimulation and submitted a related patent application (PCT/CA2020/051047).

Poster

PSTR465: Motor Learning in Animals

Location: MCP Hall A

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Program #/Poster #: PSTR465.14/I12

Topic: E.04. Voluntary Movements

Support: R01NS109361 (to L.L.)
U01 NS115588 (to C.X.)
R01NS102917 (to C.X.)

Title: Long-term Neural population Dynamics Tracking in Freely Moving Mice During Motor Skill Learning via Ultra-flexible, High-density Electrodes

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Abstract: Motor skill learning is a critical ability, but the precise evolution of neural representation and its stability throughout long-term skill learning remains understudied. A significant challenge is the lack of tools that can longitudinally track corresponding neural activity at single-neuron resolution across a broad population and resolving the rapid dynamics during movements. In our study, we employed high-density, ultra-flexible nanoelectronic threads (NETs) and implanted them in the rostral forelimb area (RFA) of the motor cortex in mice. This allowed us to track the same neural ensemble dynamics during a single-pellet reach and grasp task over weeks. The mice, which roamed freely with minimal experimenter interference in a customized automatic apparatus, showed an increase in task success rate from 20% to 60% over two weeks of training. We tracked and quantified the reach kinematics using DeepLabCut, while simultaneously recording the spiking activity of hundreds of neurons in five mice. We analyzed both single-neuron modulation to movement and the evolution of population-level representational geometry across training days. Most neurons showed heterogeneous tuning to movement during learning, while a subset displayed consistent tuning and gain modulation as the skill became more proficient. The neural manifold extracted from the dynamics of this subset showed a stable topology, but with gradual geometric drift. To further understand the evolution of neural dynamics, we compared the temporal structure of computation in the neural circuits formed by this subset of neurons using Dynamical Similarity Analysis (DSA) throughout the long-term learning process. After the skill is acquired, the single neuron tuning becomes stable and the neural population representation is reproducible across days. By quantitatively characterizing the evolution of neural representation in long-term learning behavior, we can decode movement kinematics with increased accuracy and stability. This study underscores the importance of neural plasticity and stability during and after learning for motion decoding, paving the way for future developments in adaptive brain-computer interfaces.

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Poster

PSTR466: Neuroprosthetic Strategies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.01/I13

Topic: E.05. Brain-Machine Interface

Support: DOE Grant DE-SC0022150

Title: Quantifying the spatial stability of sensory stimulation project fields for neuroprostheses

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Abstract: Recent neuroprosthesis developments have demonstrated that electrical stimulation elicits somatosensory percepts in individuals with amputations or spinal cord injuries. As the goal is to provide long-term sensory feedback, stability of the technology has become a key objective for translation to the clinic and users' home. A growing number of studies suggest that the projected fields (PFs), the locations of perceived sensations elicited by stimulation, are relatively consistent over the study period. However, there has been little focus on characterizing this spatial stability. Quantifying PF spatial stability over time will objectively confirm that the stimulation design properly serves long-term goals, thus advancing towards translation for independent use.

Here, we present a quantitative framework that determines the spatial stability of PFs. We combined the overall frequency of activation of each PF and its co-occurrence with other PFs. We designed the framework using PFs obtained from two different electrical stimulation techniques. The first used non-invasive transcutaneous electrical nerve stimulation (TENS). Surface electrodes were placed on the residual limb of an individual with upper limb amputation to activate their underlying nerves. The second applied intracortical microstimulation (ICMS) to the primary somatosensory cortex of an individual with spinal cord injury. There were 96 electrodes (3 microelectrode arrays, 32 electrodes each) across the left and right somatosensory cortices.

We find that for PFs that were not frequently elicited, the framework properly distinguished between when PFs co-occurred with other PFs versus when they did not. To assess the implications of including PF spatial properties in our metric, we incorporate tactile innervation

densities of the hand (glabrous skin and dorsum) and test our metric as a function of the geodesic distance between PFs. Furthermore, we investigate the spatial stability of functionally relevant PFs. This PF subset is determined based on hand contact regions involved in exploration and manipulation tasks. Preliminary analysis on the ICMS dataset shows high co-occurrence scores for the thumb, index, and ring fingertips.
Our results indicate that this quantitative framework can generalize to PFs elicited from different sensory stimulation techniques. Our framework bridges the gap between the intuition of PF stability and the experimental data towards a more systematic assessment of the efficacy of sensory neuroprostheses for long-term use.

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Poster

PSTR466: Neuroprosthetic Strategies

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Topic: E.05. Brain-Machine Interface

Support: NSERC
New Frontiers in Research Fund
IVADO

Title: Parallel bayesian optimization of multi-target neurostimulation for evoking diverse movements

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Abstract: Approximately 6 million individuals in North America live with paralysis after neurotrauma. While neurostimulation offers a promising avenue for restoring motor functions, its efficacy relies on finely tuning numerous parameters to suit everyone's unique needs. Bayesian Optimization (BO) based on Gaussian Process (GP) has emerged as a successful approach for efficiently optimizing neurostimulation parameters in real-time. However, existing methods are tailored to evoke single target movements, whereas everyday activities necessitate a diverse range of movements. This study aims to extend the GPBO framework to enable the optimization of neurostimulation for two or more motor outputs in parallel.
Our central inquiry revolves around the optimal distribution of trial-and-error queries (stimulation attempts) to identify all movement targets in parallel. We propose two novel BO strategies for allocating queries between 2+ models, via the Upper Confidence Bound (UCB) acquisition function: Alternate UCB and Combined UCB weighting and compare their efficacy

against sequential and single UCB targeting. To validate the robustness of our method, we consider optimization of various electromyography responses from different scenarios, including a published dataset, cortical stimulation in three male capuchin monkeys and two male macaques (96 stimulation sites and 3-4 target movements per subject), as well as a novel dataset of spinal cord (SC) stimulation in four female rats (64 sites and 4 target movements each).
For two, three and four target movements, Alternate UCB outperformed the other strategies. For four target movements, the Alternate strategy exhibits a median exploration score of 0.83. In comparison, the Combined strategy has a median of 0.78, the Sequential strategy a median of 0.73, and the Single strategy a median of 0.68. However, the Combined strategy demonstrates less variability, with an interquartile range from 0.72 to 0.85, while the Alternate strategy shows a wider range (from 0.74 to 0.92).
The Alternate UCB strategy exhibits robustness and consistency across various scenarios and datasets, efficiently identifying globally optimal electrodes or most parallel-optimized targets. Thus, integrating this strategy into the GPBO framework could offer a solution for targeting different movements simultaneously.

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Poster

PSTR466: Neuroprosthetic Strategies

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Meta Reality Labs Award #2990450277899571

Title: Algorithm-agnostic improvements in neural and myoelectric decoder performance through enhanced training data

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Abstract: Up to 50% of upper-limb prostheses are abandoned, often citing a lack of intuitive and reliable control as one of the leading reasons. Intuitive regression control of prostheses relies on

training algorithms to correlate biological recordings to motor intent. The quality of the training dataset is critical to run-time regression performance, but accurately labeling intended hand kinematics after hand amputation is challenging and the best practices to collect training data are unclear. In this work, we explored how the data collection approach and training speed impact the performance of myoelectric prostheses. In the first study, we quantified the accuracy and precision of labeling hand kinematics using two common training paradigms: 1) mimic training, where participants mimic predetermined motions of a prosthesis, and 2) mirror training, where participants mirror their contralateral intact hand during synchronized bilateral movements. We first explored this question in healthy non-amputee individuals where the ground-truth kinematics could be readily determined using motion capture (N=7). Kinematic data showed that mimic training fails to account for biomechanical coupling and temporal changes in hand posture. Additionally, mirror training exhibited significantly higher accuracy and precision in labeling hand kinematics. These findings suggest that the mirror training approach generates a more faithful, albeit more complex, dataset. Accordingly, mirror training resulted in significantly better offline regression performance when using a large amount of training data and a non-linear neural network. Furthermore, mirror training resulted in significantly faster task completion speeds and a similar subjective workload for transradial amputees completing a clothespin relocation task (N=4). In the second study, we explored the effect of training movement speed on prosthetic control (N=7). Initial findings show that the training movement speed has a significant impact on offline regression performance, for both linear (Kalman filter) and non-linear (long short-term memory network) algorithms that include a state model. Although non-significant, a trend suggests that training movement speeds can also impact the run-time performance of non-linear algorithms (convolutional neural network) without a state model. Together, these results highlight the importance of training data on the run-time performance of myoelectric prosthetic control. Consequently, these findings serve as a valuable guide for the next generation of myoelectric and neural prostheses leveraging machine learning to provide more dexterous and intuitive control.

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Poster

PSTR466: Neuroprosthetic Strategies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.04/Web Only

Topic: I.08. Methods to Modulate Neural Activity

Support: 2022M3C1A3081294
2020M3H2A107804521

Title: Modeling of Collective Neural Interactions relevant to Hemodynamics in the Spinal Cord via Neurostimulation

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Abstract: Neuromodulation, employing techniques such as Vagus nerve stimulation (VNS) and Deep brain stimulation (DBS), represents a significant advancement in treating various disorders without resorting to pharmacological interventions. The emergence of closed-loop stimulation allows for tailored treatment regimens based on patient biomarkers, thereby enhancing treatment efficacy and safety. In this study, our objective was to devise an effective neuromodulation strategy for blood pressure regulation using digital biomarkers. Specifically, our investigation centered on the potential of spinal Intermediolateral nucleus (IML) stimulation for blood pressure control. Through meticulous animal experiments and digital modeling, we explored the intricate relationship between IML neural activity and hemodynamics, with a particular emphasis on accurately predicting blood pressure changes. Our findings unveiled a spectrum of responses among neurons to stimulation, highlighting the significance of collective dynamics over individual reactions. Leveraging Principal Component Analysis (PCA) for dimensionality reduction, we identified a ring-shaped manifold highly correlated with blood pressure. Intriguingly, this manifold exhibited nonlinear characteristics, suggesting its utility as a predictive tool. By harnessing this digital biomarker approach, we achieved remarkable results, with over 80% accuracy in blood pressure estimation. This underscores the potential of our methodology for enabling continuous control of complex neural networks. Importantly, our research not only provides insights into the mechanisms underlying neuromodulation but also lays the groundwork for advancing precision medicine approaches in treating conditions requiring sustained intervention. Our study enriches the neuromodulation literature by revealing the complex interplay between neural activity and physiological outcomes. Through innovative techniques, we shed light on digital biomarkers' potential to revolutionize therapies. In conclusion, our research highlights neuromodulation's transformative potential in precision medicine. Integrating digital biomarkers into protocols enables personalized therapies, promising advancements in disorder treatments.

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Poster

PSTR466: Neuroprosthetic Strategies

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.05/I16

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant U01

Title: Intra-spinal microstimulation of the mouse lumbar spinal cord using ultraflexible electrodes

Authors: *J. ZHANG[1,2], Y. WU[1,2], L. DE LA PALMA PIEDRAS[3,2], S. WANG[4,2], C. XIE[1,2,5], L. LUAN[1,2,5];
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Abstract: Intra-spinal microstimulation (ISMS) is a valuable tool for both scientists and engineers, offering mechanistic studies of the response characteristics of local spinal cord neurons and circuits in-vivo as well as potentials for high-resolution stimulation treatments of spinal cord injuries and other motor deficits. However, due to technological limitations, previous studies have mostly been conducted in anesthetized or highly constrained animals. This approach overlooks the dynamics of motor behaviors, which are integral to these applications and may influence the effect of ISMS on local spinal circuit. In this study, we investigate the effect of temporally synchronizing ISMS with natural behavioral states on the neural activation and behavioral outcome in the mouse lumbar cord. This study also contributes to understanding the spinal cord interneuron population dynamics from an electrophysiological point of view. We leverage ultraflexible intraspinal electrodes, the nanoelectronic threads (NETs), for concurrent recording and stimulation during unrestrained motor behaviors. We find that single pulse stimulation no greater than 2nC/phase elicited robust neural activation. Stimulation of different channels along the dorsal-ventral axis yielded distinctive activation pattern and well-separated neuron-populational trajectories after dimensionality reduction of single-unit spiking activities, with mild day-to-day fluctuations and overall stability. Preliminary results suggest that the strength of modulation is dependent on the site of stimulation. Pulse-train stimulations elicited a spectrum of hind limb movements including stepping, limb flapping and muscle contraction at low currents with considerable trial-to-trial variability. In order to mitigate variability in pre-stimulation baseline neural state, we implement closed-loop stimulation using real-time behavioral markers, controlling the behavioral state for each stimulation. This paradigm will help reveal how the spinal cord neural circuitry along the dorsal-ventral axis reacts and adapts to perturbation during rhythmic activity. These ongoing efforts underscore the critical interplay between ISMS and behavior. Our study holds implications for advancing the stimulation paradigm for both basic scientific investigation and potential translational applications.

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Poster

PSTR466: Neuroprosthetic Strategies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.06/I17

Topic: I.08. Methods to Modulate Neural Activity

Support: CIHR

Title: Selectivity of motor cortex neuromodulation strategies in rats: a comparison of epidural and intracortical stimulation for alleviating walking Deficits

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Abstract: In intact rats, both intracortical and epidural stimulation of the hindlimb motor cortex demonstrate the ability to elicit hindlimb movement, and modulate gait kinematics when delivered during locomotion. Hence, this technique holds promise for alleviating walking deficits following spinal cord injury. However, it is essential to assess the trade-off in selectivity when opting for epidural stimulation over intracortical stimulation. Our study evaluated the feasibility and selectivity of employing each type of stimulation in rats with unilateral hemisection injury at thoracic level. During the experiments, a 40 ms pulse train of stimulation at a frequency of 330 Hz was applied either on the cortical surface or directly into layer V of the motor cortex following the toe off while the rats were walking on a treadmill at a speed of 23cm.s^{-1}. The amplitude was adjusted to the level that elicited the highest step height during gait, with an amplitude comfortable to the rat, determined as the subject's willingness to continue walking with stimulation to receive a food reward. Intracortical stimulation of the motor cortex resulted in a significant increase in step height during treadmill walking across rats with varying lesion severities (+ 121.87 ± 80 %; p-value < 0.05, in rats with normal hemisection). However, while epidural stimulation of the motor cortex significantly increased the step height during treadmill walking in rats with milder injuries that preserved the crossed corticospinal tract (+85 ± 44% stimulation vs spontaneous; p-value < 0.05), it failed to produce similar effects in rats with more extensive injuries that disrupted the crossed corticospinal tract (0.60 ± 0.16 cm, spontaneous walking; 0.64 ± 0.24 cm, with stimulation; p-value = 0.28).Epidural stimulation elicited off-target motor effects that were mitigated with intracortical stimulation delivery. Among others, epidural stimulation caused neck, trunk and forelimb responses resulting in a significant displacement of the head 100 ms after the stimulation delivery compared to its pre-stimulation position during treadmill walking in rats (-10.05% ± 9.99, p-value<0.01, in rats with normal hemisection).We propose that the superior efficacy of intracortical stimulation in evoking appropriate leg movements in spinal cord injured rats is linked to its higher selectivity in generating on-target motor responses, especially leg flexion. Conversely, epidural stimulation of the hindlimb motor cortex led to a variety of off-target motor effects. Ultimately, intracortical stimulation proves to be more effective in addressing walking deficits across rats with varying degrees of injury severity.

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Poster

PSTR466: Neuroprosthetic Strategies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.07/Web Only

Topic: E.05. Brain-Machine Interface

Title: Hci technologies in rehabilitation: enhancing physical therapy with semg, vr and llm-generated music

Authors: *Y. WU, Y.-J. SU, J.-B. LU, Y. WANG, T.-H. CHEONG;
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Abstract: Home-based rehabilitation can save the cost of travel and time, however, the low willingness of participation groups appear among patients caused by the repetitive rehabilitation activities, loneliness, and isolation (Nguyen et al., 2021). Moreover, the absence of real-time objective metrics to evaluate individual neurorehabilitation performance could decrease the effectiveness in daily activities. Therefore, an interactive AI-coach and game-like user interface to analyze users' real-time neurophysiological movement are crucial in developing a home-based rehabilitation system.We propose an interactive rehabilitation system that consists of surface electromyography (sEMG) and large language models (LLM)-generated in a game-like interface in the virtual reality (VR). The system creates a virtual online platform allowing patients to interact with their rehabilitation partners or therapists in real-time. From a music theory standpoint (Barthet et al. 2014), users were asked to perform four poses in one set for a pleasant chord structure. Visual prompt would be shown to users and once the full set of poses is completed, the chosen chords will then be a reference for prompted-LLM to generate a well-organized musical melody as a feedback. EMG signals provide important information of neuromuscular disorders (Reaz et al.,2006). Three electrodes are placed at the brachioradialis, biceps, and deltoids on one arm to monitor upper limb muscular activity, corresponding to notes that will be matched to a specific musical chord. We utilize support vector machine (SVM) in decoding the sEMG signals to recognize upper limb gestures, and ensuring the quality of rehabilitation.The preliminary results demonstrated the feasibility of using the SVM model to decode upper limb muscular activity during rehabilitation. Also, users reported increasing excitement and enjoyment compared to conventional rehabilitation. The results depict the potential effectiveness of the proposed system and led to an early-stage assumption that our system would heighten the motivation of patients participating in rehabilitation.(Nguyen et al., 2021)We present an interactive system capable of decoding real-time sEMG signals, generating musical melody through prompted-LLM, and providing an immersive VR environment. The platform aims to enhance the willingness of completing rehabilitation therapy, and improving telehealth quality and accessibility. Future study will focus on refining the system and

conducting larger-scale clinical trials with questionnaire and neurofeedback to ameliorate the system versatility and user experience.

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Poster

PSTR466: Neuroprosthetic Strategies

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Program #/Poster #: PSTR466.08/I18

Topic: E.05. Brain-Machine Interface

Support: National Science Foundation Grant CAREER 1845348

Title: Impact of functional connectivity in scalp EEG on motor imagery task decoding

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Abstract: The functional connectivity of the brain as retrieved from multichannel scalp EEG has recently gained attention to classify motor imagery (MI) tasks in brain-computer interface (BCI) applications. Studies combining connectivity features with deep learning models have reported promising accuracies in decoding MI tasks. However, it remains unclear (i) how BCI decoders based on connectivity measures perform compared to decoders based on single-channel power features, (ii) which connectivity measures enhance the decoding accuracy the most, and (iii) how the EEG-based brain network evolves across MI tasks. Our study addresses questions (i)-(iii) by analyzing two public datasets of binary MI tasks, i.e., the BCI Competition IV dataset 2a and the PhysioNet MI dataset. Connectivity measures of EEG channels included Phase Locking Value (PLV), Granger causality, weighted Phase Lag Index, and cross-correlation, and Random Forests classifiers were applied to the connectivity matrices to determine the separability between MI tasks. Regarding (i)-(ii), a permutation test was used to determine the significance of connectivity-based classification, and we found that connectivity measures can discriminate between tasks (*P*-value $P<0.01$) in 8 out of 9 (Competition IV) and 92 out of 109 (PhysioNet MI), with the PLV consistently outperforming the other connectivity measures and reaching classification performance comparable to power features. Moreover, the centrality of the nodes in the PLV-based connectivity networks correlates strongly with the channel importance in power-based classification, thus indicating that channels with the highest change in power during motor imagery are also integral to the information flow across the brain network during such tasks. Regarding (iii), we found that, even though the strategies for motor imagery can vary across participants and produce subject-specific brain networks, the edges spanning the motor region have the highest predictive value in MI task decoding across subjects. Also, while the topology of the brain network as measured by Graph Density, Shortest Path Length, and Clustering Coefficient, did not significantly change during right- vs. left-hand MI tasks, we found that a small set of connections, i.e., top 14% in the BCI Competition dataset and top 3% in

the PhysioNet dataset, was significantly modulated in left- vs. right-hand imagery and drove the classification of tasks. Altogether, our study highlights the role of functional connectivity in MI and the relationship between brain graph properties and single-channel spectral content. These results can provide groundwork for enhancing BCI applications.

Disclosures: F. Delavari: None. **S. Santaniello:** None.

Poster

PSTR466: Neuroprosthetic Strategies

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR466.09/I19

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R00MH128772

Title: Super-resolving surface recordings of the human cortex

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Abstract: Mobile non-invasive neuroimaging technologies such as electroencephalography (EEG) and functional Near-Infrared Spectroscopy (fNIRS) facilitate the recording of neural states in naturalistic settings. Despite their ease of use and minimal overhead, these modalities face significant resolution limitations. EEG is hampered by poor spatial resolution and susceptibility to noise artifacts, whereas fNIRS is limited by poor temporal resolution and a delayed hemodynamic response. It is also widely acknowledged that the majority of the signals captured by fNIRS and EEG are non-neural. Thus, denoising and up-resolving could improve the efficacy of non-invasive brain-computer interface applications. Previous approaches have tried to mitigate these issues through combining simultaneous fNIRS and EEG recordings (Li et al. 2022), or up-sampling through super-resolving one modality (Owen et al. 2020). This study proposes developing a joint multivariate auto-regressive model of EEG and fNIRS recordings. This model aims to learn the covariance between the EEG signal at any given time and neighboring time points across all fNIRS channels. By parameterizing a full joint distribution of EEG and fNIRS signals across the brain at discrete spatial locations, this model facilitates the translation of fNIRS signals from EEG signals and vice versa, while also creating a common latent space that encodes a shared neural signal. This methodology was applied to a dataset comprising simultaneous recordings of fNIRS (36 channels) and EEG (30 channels) from 26 participants engaged in working memory tasks (Shin et al. 2018). The study encompassed multiple cortical regions including prefrontal, motor, parietal, and occipital areas, with a spatial resolution of approximately 3 cm. Analysis revealed that fNIRS and EEG exhibit a temporally varying correlation that differs between individuals and optode locations. This correlation was essential for effectively enhancing the resolution of the modalities. The model demonstrated a

denoising capability for EEG based on fNIRS data and achieved a reconstruction accuracy of up to 0.6 R-squared. This result is proven reproducible across different individuals, indicating the feasibility of generalizing this approach to a wider population.

Disclosures: M. Middleton: A. Employment/Salary (full or part-time):; Northrop Grumman Software Engineer. **E. Varol:** None.

Poster

PSTR466: Neuroprosthetic Strategies

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Biological Input/Output Systems
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Title: Enhancing neuroprosthesis calibration: The advantage of integrating prior training over exclusive use of new data

Authors: *C. J. THOMSON[1], T. N. TULLY[1], E. S. STONE[1], C. B. MORRELL[4], E. SCHEME[4], D. J. WARREN[1], D. HUTCHINSON[2], G. A. CLARK[1], J. A. GEORGE[3]; [1]Biomed. Engin., [2]Dept. of Orthopaedics, [3]Electrical Engin., Univ. of Utah, Salt Lake City, UT; [4]Inst. of Biomed. Engin., Univ. of New Brunswick, Fredericton, NB, Canada

Abstract: Neuroprostheses typically operate under supervised learning, in which a machine-learning algorithm is trained to correlate neural or myoelectric activity with an individual's motor intent. Due to the stochastic nature of neuromyoelectric signals, algorithm performance decays over time. Neuroprostheses and commercial myoelectric prostheses are often recalibrated and retrained frequently so that only the most recent, up-to-date data influences the algorithm performance. Here, we introduce and validate an alternative training paradigm in which training data from past calibrations is aggregated and reused in future calibrations. Using a cohort of four transradial amputees implanted with intramuscular electromyographic recording leads, we demonstrate that aggregating prior datasets improves prosthetic control in offline analyses and an online human-in-the-loop task. In offline analyses, we compared the performance of a convolutional neural network (CNN) and a modified Kalman filter (MKF) to simultaneously regress the kinematics of an eight-degree-of-freedom prosthesis. Both algorithms were trained under the traditional paradigm using a single dataset, as well as under the new paradigm using

aggregated datasets from the past five or ten trainings. In online analyses, we tested this new paradigm by aggregating up to three datasets and comparing performance on a virtual-target-touching task to the standard daily retraining paradigm. Dataset aggregation reduced the root-mean-squared error of algorithm estimates in offline analyses for both the CNN and MKF, although the CNN saw a greater reduction in error. Further offline analyses revealed that dataset aggregation improved CNN robustness when reusing the same algorithm on subsequent test days, as indicated by a smaller increase in root mean squared error per day. Finally, data from an online virtual-target-touching task with one amputee showed significantly better real-time prosthetic control when using aggregated training data from just two prior datasets. Altogether, these results demonstrate that training data from past calibrations should not be discarded but, rather, should be reused in an aggregated training dataset such that the increased amount and diversity of data improve algorithm performance. More broadly, this work supports a paradigm shift for the field of neuroprostheses away from daily data recalibration for linear algorithms and towards daily data aggregation for non-linear algorithms.

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Poster

PSTR466: Neuroprosthetic Strategies

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Topic: E.05. Brain-Machine Interface

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This work is also supported by the Valencian Graduate School and Research Network of Artificial Intelligence (ValgrAI), Generalitat Valenciana and European Union.

Title: Decoding motor imagery of starting walk with a lower-limb exoskeleton by using EEGnet and TSNE

Authors: J. GARCÍA-VILLALÓN[1], P. SORIANO-SEGURA[1], M. ORTIZ[1], E. IÁÑEZ[1], ***J. M. AZORIN**[1,2];
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Abstract: Motor imagery (MI) is the mental practice of a movement without physically performing it. MI can facilitate physical rehabilitation and promote motor learning through neuroplasticity mechanisms. This paper studies the detection of the MI for starting the gait with a lower-limb exoskeleton regarding a basal state with the help of a brain-machine interface (BMI) based on EEG signals for 4 subjects.
The experimental protocol consisted of 7 trials composed of two basal state periods of 7 s, separated by one MI period of 14 s, in which subjects had to imagine starting to walk while wearing a lower-limb exoskeleton. An auditory signal indicated the transitions. This protocol was applied to each subject for 5 sessions on consecutive days. Figure shows the experimental setup.
Data analysis of the 32 recorded channels was performed in epochs of 2 s every 0.5 s. Each epoch was preprocessed with: Notch (50 Hz), HPF (1 Hz) and an eye artefact filter from 4 EOG channels. The remaining 28 EEG channels were: AF3, F3, FZ, FC3, FC1, FCZ, C5, C3, C1, CZ, CP3, CP1, CPZ, P3, PZ, PO3, AF4, F4, FC2, FC4, C2, C4, C6, CP2, CP4, P4, POZ, PO4. Finally, a CAR and BPF filter (8-40 Hz) was applied.
Decoding was performed using the deep learning EEGnet neural network. It was tested with the base architecture (B) and with a small adaptation of the proposed network (A), which differs in the modification of the output layers of the network with a focus on the use of TSNE (T-distributed Stochastic Neighbor Embedding). The average results of accuracy of the 4 subjects in (B, A) were: (87.45%±7.87, 89.75%±5.75), (68.67%±9.42, 71.33%±9.00), (60.56%±12.18, 62.50%±9.74), (61.63%±11.89, 64.23%±14.26).
In conclusion, an improvement in the accuracy of MI decoding was observed in all 4 subjects and a reduction of the standard deviation in 3 of them.

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Poster

PSTR466: Neuroprosthetic Strategies

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Title: Restored Plantar Sensations Enhance Trip Recovery in Individuals with Lower Limb Amputation

Authors: *S. LI[1,2], R. J. TRIOLO[1,2], H. CHARKHKAR[1,2];
[1]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [2]Louis Stokes Cleveland Veterans Affairs Med. Ctr., Cleveland, OH

Abstract: Over half of individuals with lower limb amputation report a fear of falling and subsequently avoid daily activities, partly attributed to loss of plantar sensory feedback. In this study, two individuals with unilateral transtibial amputations (LL1 and LL2) and one with knee disarticulation (LL3) received an implanted sensory neuroprosthesis (SNP). This system electrically activates the residual nerves via cuff electrodes to elicit plantar sensations co-located with prosthesis foot-floor interactions detected from a force-sensing insole. Our prior work shows that the SNP enhances gait stability, aids in navigating complex terrain, and improves limb speed perception. Here, we investigated the effects of the SNP on stumble recovery and fall avoidance. Participants walked on a split-belt treadmill at their preferred speed while perturbed by sudden acceleration of the treadmill belts. Perturbations were initiated during early stance randomly on the intact and prosthetic sides. Data were collected from a motion capture system and force plates embedded in the treadmill. A repeated measures ANOVA determined the effect of the SNP across recovery steps on the outcome measures. With SNP active, two participants (LL1 and LL3) exhibited reduced peak trunk flexion angular velocities during intact (LL1: $p=0.016$, LL3: $p<0.001$) and prosthetic (LL1: $p<0.001$, LL3: $p<0.001$) side perturbations, indicating improved trunk control and enhanced stability. For intact side perturbations, peak ground reaction force magnitudes (|GRF|) during the first recovery step with the prosthetic leg increased with SNP active (LL1: $p=0.006$, LL3: $p<0.001$). This approached the already greater peak |GRF| during the first recovery step with the intact side following a prosthetic side perturbation. The more symmetric recovery pattern suggests the SNP instilled a greater confidence in using their prosthetic leg during recovery. Conversely, peak |GRF| decreased for prosthetic side perturbations with SNP active (LL1: $p=0.003$, LL3: $p<0.001$), indicating participants required less force to arrest forward rotation. Notably, LL2 did not exhibit changes with SNP active; however, his smaller trunk flexion angular velocities compared to other participants suggest a higher overall stability. As such, stronger perturbations might be necessary to sufficiently challenge his stability to observe a SNP effect. These results suggest restored sensory feedback by the SNP can be effectively integrated into the sensorimotor control system of individuals with lower limb amputation, improving the ability to stabilize after an induced trip and potentially reducing fall risk.

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Poster

PSTR466: Neuroprosthetic Strategies

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Topic: I.08. Methods to Modulate Neural Activity

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Title: Selective peripheral nerve modulation via custom epineural cuffs and temporal interference stimulation

Authors: M. RILEY[1], F. TALA[2], K. J. JOHNSON[3], *B. C. JOHNSON[2];
[1]Biomed. Engin. Doctoral Program, [2]Electrical and Computer Engin., [3]Office of Res. Compliance, Boise State Univ., Boise, ID

Abstract: The need for non-pharmaceutical therapies for neurological conditions resistant to traditional treatments has spurred advanced neuromodulation techniques. Spatially selective stimulation of peripheral nerves in bioelectronic medicine potentially reduces adverse effects from nonspecific nerve activation. Temporal interference (TI) stimulation, previously used in central nervous system applications, is emerging as a promising method for selective modulation without intraneural electrodes. Prior TI research suggests that superimposing high-frequency currents (≥1 kHz) with slight frequency offsets (Δf = 1-50 Hz) can modulate neural activity at the envelope frequency, Δf. This study investigates the application of TI to selectively stimulate the mouse sciatic using spatially variant electrical fields and benchmarking their selectivity and efficiency against spatially selective biphasic stimulation. Computational modeling using COMSOL Multiphysics determined the best spatial points to elicit targeted Δf zones within the mouse sciatic nerve. The Δf areas were scaled as small as 50 um in diameter, which was smaller than the tibial and peroneal fascicle diameters in adult C57BL/6 mice. The custom multicontact nerve cuff was implanted on the mouse sciatic nerve, proximal to the branches. The cuff consisted of eight electrodes (100 um diameter), coated with PEDOT:PSS to improve charge injection capacity. To measure selective activation of the tibial and peroneal bundles, we recorded electromyography (EMG) from the lateral gastrocnemius and tibialis anterior muscles, respectively. The targeted region was specified through the spatial selection of electrode pairs on the cuff. EMG responses to biphasic stimulation showed typical peak selectivity indices (SI) (≤1) for the two muscle groups of 0.79 and 0.92, respectively. In this study, we computed SI as the difference in activation of the two muscles, where one is partially to fully activated, and the other muscle is not activated at all. Ongoing TI selectivity data will be compared to biphasic SIs to validate and refine selectivity. Although further testing is needed to fully identify the biophysical mechanism of TI, this study highlights TI and multi-contact nerve cuff's potential in peripheral nerve applications and sets the groundwork for future clinical implementations.

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Poster

PSTR466: Neuroprosthetic Strategies

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Program #/Poster #: PSTR466.14/I24

Topic: E.05. Brain-Machine Interface

Support: NIH UO1 1U01NS126052-01

Title: Electrochemical Impedance Spectroscopy Analysis of Ultramicroelectrode Arrays in Neural Stimulation: A Stability Assessment

Authors: *Q. DONG[1], C. ELUAGU[1], Y. WU[2], E. OLIVO[1], P. MORALES VÁSQUEZ[1], J. HETKE[3], S. S. COGAN[4], M. ORAZEM[1], K. J. OTTO[5];
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Abstract: Novel neural interfaces, particularly microelectrode arrays (MEAs) and ultramicroelectrode arrays (UMEAs), hold promise for enhancing microstimulation (μStim) applications within the brain. These technologies aim to precisely activate neurons without damaging the electrode or tissues, crucial for designing long-term brain-machine interfaces (BMIs). Our research focuses on evaluating the safety and efficacy of MEAs and UMEAs using Electrochemical Impedance Spectroscopy (EIS) techniques. We custom-built the first-generation (G1) electrode arrays from NeuroNexus Technologies, Inc. (Ann Arbor, MI), constructed on a silicon substrate with gold contacts coated in Sputtered Iridium Oxide Film (SIROF). The arrays featured four 3 mm-long, 15 μm-thick shanks, each with eight electrodes ranging from 5 to 50 μm in diameter. EIS was performed using an Autolab PGSTAT12 with a three-electrode setup, across a frequency range of 1 Hz-100 kHz in a phosphate-buffered saline (PBS) solution. We implanted G1 devices into the rat somatosensory cortex, followed by electrical stimulation at 0 and 0.4 nC/phase, with 20 repetitions at a frequency of 3 Hz. EIS data showed that larger electrodes (40 and 50 μm) exhibited an increase in post-stimulation impedance, indicating stability with slight variability. Most electrodes maintained impedance close to pre-stimulation levels. Accuracy contour plots generated from the second-generation (G2) device comparisons validated the EIS system's precision across the studied frequency range, confirming operational accuracy within specific impedance boundaries. The study demonstrated the stability of G1 devices, affirming their potential for reliable long-term neuromodulation. The detailed accuracy contour plots provided essential validation of the EIS system, supporting further optimization and use of UMEAs in advanced neural interface applications.

Disclosures: Q. Dong: None. **C. Eluagu:** None. **Y. Wu:** None. **E. Olivo:** None. **P. Morales Vásquez:** None. **J. Hetke:** None. **S.S. Cogan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Qualia Oto. F. Consulting Fees (e.g., advisory boards); Qualia Oto. **M. Orazem:** None. **K.J. Otto:** None.

Poster

PSTR466: Neuroprosthetic Strategies

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Program #/Poster #: PSTR466.15/I25

Topic: E.05. Brain-Machine Interface

Support: NIH UO1 1U01NS126052-01

Title: Chronic Intracortical Microstimulation with Ultramicroelectrode Arrays Via Spatial Current Steering

Authors: E. M. OLIVO[1], Y. WU[2], W. M. GRILL[3], S. F. COGAN[4], M. ORAZEM[5], ***K. OTTO**[1];
[1]Purdue Univ., West Lafayette, IN; [2]Material Sci. Engin., Univ. of Texas at Dallas, Dallas, TX; [3]Duke Univ., Durham, NC; [4]Bioengineering, The Univ. of Texas at Dallas, Dallas, TX; [5]Univ. of Florida, Gainesville, FL

Abstract: Chronic neurostimulation devices often encounter challenges due to the body's inflammatory response, resulting in device encapsulation and signal degradation over time. Ultramicroelectrode arrays (UMEAs) with subcellular dimensions have been designed to improve biocompatibility and stability during chronic stimulation. However, smaller electrode sites lead to higher current densities, potentially causing damage to the device or surrounding tissue. To address this challenge, multiple electrode sites can deliver effective stimulation simultaneously and reduce the charge on each electrode site. Ultramicroelectrode devices were custom designed with 26 electrodes of 5 µm and 10 µm diameters (19.63 μm^2 and 78.54 μm^2, respectively). To improve charge-storage capacity, electrodes were coated with a sputtered iridium oxide film (SIROF). The electrodes were implanted to a depth of 1700 µm in the somatosensory cortex. Stimuli were delivered to electrode sites with the total charge injected per electrode site limited to 0.8 nC/phase for 5 µm diameter sites and 2.4 nC/phase for 10 µm diameter sites. A modified conditioned avoidance behavioral paradigm [1] was used to determine detection thresholds in rats. Water-deprived rats were monitored for licking patterns, with safe trials (controls) and warning trials (ICMS stimulus). Detection thresholds were determined with an adaptive algorithm that adjusted stimulus amplitude based on animal performance. Chronic behavioral responses to neural stimulation were observed, with consistent thresholds achieved by stimulating multiple channels simultaneously. In one subject, the average charge per phase per electrode for various combinations of 10 µm diameter sites was 1.16 nC/phase, while the average total charge applied was 5.20 nC/phase. Stimulating multiple channels simultaneously yields effective chronic stimulation. Additionally, reducing the electrode site area stimulated shows promise in improving stimulation efficacy. These insights highlight the feasibility of multi-channel intracortical microstimulation and pave the way for further innovations in brain-machine interface technology to enhance sensory feedback for persons with paralysis. [1] J. B. Kelly et al., “Behavioral limits of auditory temporal resolution in the rat: Amplitude modulation and duration discrimination,” J. Comp. Psychol., vol. 120, pp. 98-105, May 2006.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

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Program #/Poster #: PSTR467.01/Web Only

Topic: E.06. Posture and Gait

Title: Sex and age differences in postural stability under different visual conditions

Authors: S. GUARDUCCI[1], G. PANCONI[2], V. SORGENTE[2], *D. MINCIACCHI[2], R. BRAVI[2];
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Abstract: Postural control is essential for optimal performance of many daily activities and depends on the integration of sensory input, such as visual information. Older adults showed impaired postural control compared to young subjects due to their inability to effectively use visual input. However, the differences in postural sway between sexes within young and older adults remain unclear, with numerous studies reporting conflicting results. Intermittent perturbations of the visual system have been recently employed in young and old people for postural control assessment and balance interventions, but much is still unknown regarding how disrupted vision affects postural control. The present study aimed to investigate the influence of sex and age on postural sway, and whether the effect of an intermittent visual perturbation on postural control is sensitive to these two factors. 20 young adults (10 males and 10 females) and 18 older adults (10 males and 8 females), free of musculoskeletal, neurological, and visual disorders, were recruited. Subjects performed 3 trials of double-limb stance under the following visual conditions: eyes open, eyes closed, and stroboscopic vision (SV). SV was completed with specialized eyewear that intermittently cycled between a transparent state of 100 ms and an opaque state of 344 ms. Postural tasks were performed on firm and foam surfaces, with the order randomized across visual and surface conditions. The following center of pressure parameters were analyzed: transversal range, longitudinal range, sway path, sway area and mean sway velocity. Our results suggest that females exhibited larger postural sway compared to males. In young adults such differences were observed when subjects were totally deprived of visual control on a firm surface, and with a total or partial visual occlusion on a foam surface. In older adults the differences were noted when vision was absent or partially removed on a firm surface, and in all visual conditions on a foam surface. In addition, older males showed greater postural instability compared to young males on both firm and foam surfaces, while older females reported greater postural sway than young females only on a foam surface. We also found that the effect of SV was greater in females and in olders, and it seemed to increase with the difficulty of the balance task (foam surface). Results indicate the necessity of considering sex-

and age-related differences in postural control when developing interventions aimed at compensating postural control deficits. Our study may also contribute to better understand the effect of an intermittent visual deprivation on static postural control.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

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Program #/Poster #: PSTR467.02/I26

Topic: E.06. Posture and Gait

Support: NSF EFRI BRAID 2223793

Title: Spatially-distributed population-coded network model, that integrates joint angle measurements to compute limb posture

Authors: *B. ZADOKHA, N. S. SZCZECINSKI;
Mechanical, Materials and Aerospace Engin., West Virginia Univ., Morgantown, WV

Abstract: In this study, we introduce a dynamic neural model that uses sensory receptive fields inspired by biology to compute “higher order” postural information, e.g., the forward kinematics of a robotic leg. Leveraging the SNS-Toolbox, we implement the model without the need for optimization or machine learning. Tuning synaptic conductance values is accomplished through the Functional Subnetwork Approach.To explore the impact of network construction on encoding accuracy, we systematically vary sensory neuron receptor functions, the number of sensory neurons, and neuron time constants. Model accuracy is evaluated using the root-mean-squared error metric. Notably, our findings demonstrate the superior efficiency of a multi-output model compared to employing multiple networks with singular outputs. In ongoing work, we are characterizing the resilience of our network model. We use a wide Gaussian bell curve as a sensory network activation function. This ensures that we have more than one active neuron at every timestep, so in case of losing a connection or sensory neuron, the network can calculate an output more accurately than previously when only one neuron was active. This approach requires finding a new gain for each synaptic connection between interneuron compartments and output neurons. This work will improve our understanding of how the nervous system integrates sensory inputs to compute quantities useful for postural control, as well as novel control architectures for limbed robots.

Disclosures: B. Zadokha: None. **N.S. Szczecinski:** None.

Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.03/I27

Topic: E.06. Posture and Gait

Support: NSF CRCNS 2113028

Title: Investigating how the nervous system integrates distributed force measurements using strain sensors on a robotic Carausius morosus leg

Authors: *I. M. KUDYBA[1], S. N. ZILL[2], N. S. SZCZECINSKI[1];
[1]West Virginia Univ., Morgantown, WV; [2]Biomed. Sciences/Anatomy, J.C. Edwards Sch. Med., Huntington, WV

Abstract: Animals use sensory organs to provide feedback on their motor output during standing and walking, enabling adaptive and robust behavior. One sensory organ found in insects are campaniform sensilla (CS), which are mechanosensors embedded in the cuticle that monitor resisted muscle forces. Consequently, CS discharge encodes information on forces applied on the leg. However, due to both the size of insects as well as the lack of non-invasive genetic accessibility, it is difficult to fully characterize how discharge from CS is used to aid in motor output. How could the nervous system integrate redundant strain data to encode leg loading? In this study, we perturb a robotic stick insect leg and measure the resulting strains at the locations of several CS groups. We develop a model for integrating redundant strain information from multiple locations across the leg to deduce the net external force vector acting on the leg. Then, we validate the model by comparing its estimate of each external force to the actual perturbation. These data are useful to better understand how sensory information from campaniform sensilla might be integrated from across the leg for use in posture control and locomotion. Furthermore, through the application of distributed sensors in robotic limbs, this work may aid in the design of robust and resilient robotic systems that can adapt to changes in their environment in an animal-like way.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

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Program #/Poster #: PSTR467.04/I28

Topic: E.06. Posture and Gait

Support: NSF/ECCS 2024414
NIH/NICHD R01 HD032571

Title: Length-dependent sensory feedback from proximal hindlimb muscles contributes to balance control during cat locomotion

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Abstract: Precise coordination of the swing-stance and stance-swing transitions is critical for balance control during locomotion. It has been suggested that length-dependent sensory feedback from proximal hindlimb muscles regulates these phase transitions. Thus, compromising this feedback might affect balance control and lead to compensatory motor adaptations to improve locomotor balance and stability. The goal of this study was to examine the effects of permanent removal of stretch reflex from proximal hindlimb muscles via their self-reinnervation (Cope et al., 1994) on stability of locomotion in cats. Since muscle self-reinnervation and recovery of muscle activity takes several months, we hypothesized that if stretch feedback was involved in regulation of locomotor balance, we would see locomotor adaptations that tend to increase stability. We recorded 3D full-body mechanics and EMG activity of hindlimb muscles during overground walking of adult cats before and after self-reinnervation of selected thigh muscles spanning the right hip and knee joints. For muscle self-reinnervation, nerves innervating the selected thigh muscles were surgically transected and immediately repaired. Locomotor EMG activity of these muscles recovered in 4-6 months, and the locomotor experiments were repeated. After completion of locomotion data collection, the absence of stretch reflex in self-reinnervated muscles was verified in terminal experiments (Lyle et al., 2016). We computed measures of locomotor stability that included the hindlimb and forelimb step widths, areas of support during different phases of the cycle, the durations of these phases, the static and dynamic stability margins, etc. We found that in the control condition (before muscle self-reinnervation), the forelimb step width was significantly greater than that of the hindlimb. The control animals had greater margins of stability during the 3-limb support phases with two forelimbs on the ground compared with the 3-limb support phases with two hindlimbs on the ground. This suggests that in the control condition, the forelimbs contribute more to regulation of locomotor stability than the hindlimbs. After removal of stretch-reflex from proximal muscles of only the right hind leg, we observed an increase in hindlimb step width with little or no changes in forelimb step width, an increase in the duration and area of three-limb support phases, a decrease in the duration of two-limb support phases, and an increase in margins of static and dynamic stability. These results suggest that length-dependent feedback, specifically stretch reflex, from thigh muscles is involved in balance control during cat locomotion.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.05/I29

Topic: E.06. Posture and Gait

Title: Descending vestibulospinal input influences heteronymous reflexes from quadriceps onto soleus

Authors: *A. NOGI[1], B. A. DAMEWOOD[2], C. GROVE[3], T. NICHOLS[4], M. A. LYLE[5]; [1]Emory Univ. and Georgia Inst. of Technol., Atlanta, GA; [2]Dept. of Rehabil. Med., Emory Univ. Sch. of Med., Decatur, GA; [3]Emory Univ., Atlanta, GA; [4]Biol. Sci., Georgia Technol., Atlanta, GA; [5]Div. of Physical Therapy, Emory Univ., Atlanta, GA

Abstract: The vestibular system plays an essential role in coordinating lower limb muscles to maintain posture and balance. However, whereas vestibulospinal projections are known to contribute to postural responses by activating extensor motoneurons, less is known about the potential coordinating influence mediated by vestibulospinal modulation of heteronymous spinal reflexes. Here, we used selective activation of vestibular afferents with galvanic vestibular stimulation (GVS) to examine the modulatory influence of descending vestibulospinal input on lower limb heteronymous reflexes in nine participants (25.78 $\pm$ 1.79 years). Heteronymous reflexes from the quadriceps onto soleus were examined by stimulating the femoral nerve (~30% of maximal motor response) and quantifying excitatory and inhibitory reflexes as increases and decreases in tonic soleus EMG (20% of max activation) while supine with a head neutral position.Vestibulospinal influences on heteronymous reflexes were evaluated by applying GVS 100 ms prior to femoral nerve stimulation. Additionally, heteronymous reflex activity was examined with eyes open and closed to probe whether vestibular sensory weighting changes without vision. GVS applied 100 ms prior to femoral nerve stimulation resulted in a significant decrease in soleus inhibition when compared to femoral nerve stimulation alone with eyes open (9.5% decrease, P=0.001) and closed (11.7% decrease, P=0.027). In 5 of 9 participants, the decrease in heteronymous inhibition from GVS stimulation was larger with eyes closed compared to eyes opened. There was no effect of GVS on heteronymous excitation for eyes opened or eyes closed conditions (P>0.05), though 7 of 8 participants that exhibited excitation demonstrated increased heteronymous excitation when GVS was applied with eyes opened and 5 of 8 participants with eyes closed. Our findings provide new evidence in humans that descending vestibulospinal inputs influence lower limb heteronymous reflexes in a non-weight-bearing context. The consistent reduction in heteronymous inhibition with GVS suggests that vestibulospinal projections influence inhibitory interneurons (Golgi tendon organ or Renshaw cells) or their synaptic contacts onto soleus motoneurons. Reduced heteronymous inhibition and the nonsignificant trend for increased excitation with GVS suggests that vestibular afference may facilitate ankle muscle motor output. Future study is needed to identify how the vestibular system influences lower limb heteronymous reflexes in healthy persons and those with aging- or disease-related postural instability during other postures and tasks.

Disclosures: A. Nogi: None. **B.A. Damewood:** None. **C. Grove:** None. **T. Nichols:** None. **M.A. Lyle:** None.

Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.06/I30

Topic: E.04. Voluntary Movements

Title: Self-external attribution of touched-surface motion for standing balance

Authors: *S. TAKAMUKU[1], B. STRUCKOVA[2], M. BANCROFT[2], H. GOMI[3], P. HAGGARD[2], D. KASKI[2];
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Abstract: Humans can improve standing balance by lightly touching an earth-fixed object with their hands [Jeka and Lackner, 1994]. The effect is considered to result from our implicit sensorimotor control which estimates body sways from somatosensory signals of the hand/arm and produce compensatory motor responses. The signals, however, could reflect not only self-motion but also the motion of the touched object in the environment. This raises a question whether the sensorimotor system involves a process of causal inference: whether it identifies the causes and adjusts the gain of the motor response according to the interpretation so that the response would increase when motion signals are attributed to self-motion. To address the issue, we asked the participants to stand still on an unstable surface with their vision occluded while lightly touching their right thumb against a surface which moved randomly in the anterior-posterior direction. We simultaneously measured the postural response to the surface motion and the accuracy in judging the direction of the surface motion. The attribution hypothesis assumes that the gain of postural response would be larger when the surface motion is misattributed to self-motion. In agreement with this theory, we found that the gain increases when the direction of the surface motion is misjudged. We also found that the gain and the accuracy in judging the surface motion direction show a negative correlation across trials. The attribution hypothesis also predicts that providing an additional cue which suggests that the body is not swaying would decrease the gain of the postural response and increase the accuracy in judging the surface motion direction. To test this prediction, we asked participants to touch a static surface with their left hand while experiencing surface motion with their right hand. In agreement with the prediction, the static touch caused the gain of postural response to decrease and the accuracy of surface motion perception to increase. The second experiment also replicated the negative correlation between the gain and the accuracy. Our findings suggest that a process of self-external attribution of somatosensory motion signals underlies our postural responses.

Disclosures: S. Takamuku: A. Employment/Salary (full or part-time):; NIPPON TELEGRAPH AND TELEPHONE CORPORATION. **B. Struckova:** None. **M. Bancroft:** None. **H. Gomi:** None. **P. Haggard:** None. **D. Kaski:** None.

Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.07/I31

Topic: E.04. Voluntary Movements

Title: Motor symptoms common to Huntington's, Parkinson's, and cerebellar disease can be explained by command timing volatility

Authors: *A. TAKAGI[1], H. GOMI[2];
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Abstract: While Huntington's disease (HD), Parkinson's disease (PD) and cerebellar ataxia (CA) damage the nervous system in different ways, they all impair motor timing (Bechtel et al., 2010; O'Boyle et al., 1996; Schlerf et al., 2007). Here, we show how fluctuations in motor timing explain some of the motor symptoms common to HD, PD, and CA. These include spasmodic movements (chorea), slowness (bradykinesia), poor aiming or feedforward control, and faulty feedback control in the form of excessive corrections at movement termination. First, we present evidence of volatile motor timing in two experiments with healthy participants to demonstrate how command timing volatility leads to more variable movements and forces, which cannot be explained by signal-dependent noise alone. We then built a computer simulation of a brain, which was corrupted by command timing volatility, that controlled a multi-joint arm. In this model, the planned muscle activity from each muscle was shifted in time separately to simulate the effects of volatile timing arriving from the brain. The amount of timing volatility was increased to observe its effects on reaching movements. Our model replicates the jerky movements and excessive corrections following HD and CA (Smith et al., 2000). It also predicts large aiming variability at movement onset, which has been seen in patients with HD, PD and CA (Bertram et al., 2005; Sanguineti et al., 2003). Impaired aiming cannot be explained by the feedback error control hypothesis (Smith et al., 2000), which suggests that faulty feedback corrections are to blame for the motor deficits in HD. We also used our model to observe what happens to postural control when motor timing becomes more volatile. When timing grew worse, the simulated arm generated spasmodic movements characteristic of chorea. However, slowing down the movement helped to reduce movement variability, which may explain why HD and PD patients voluntarily move slower than they can. Our theory suggests that impaired motor timing may be the underlying cause of some of the deficits in motor coordination that are shared by patients with HD, PD and CA.

Disclosures: A. Takagi: None. **H. Gomi:** None.

Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.10/I32

Topic: E.06. Posture and Gait

Support: research grant Exploratory research grant from F. Hoffmann La Roche to MC and RMF.

Title: Integration of Epidural Spinal Cord Stimulation in Complex Motor Tasks in People with Spinal Muscular Atrophy

Authors: *S. DONADIO[1,2], G. PRAT ORTEGA[3,2], S. ENSEL[4,2], A. BOOS[5,2], L. E. FISHER[6,2,7], P. GERSZTEN[3], G. Z. MENTIS[8,9,10], R. M. FRIEDLANDER[3], E. PIRONDINI[4,2,11], M. CAPOGROSSO[3,2,12];
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Abstract: Spinal Muscular Atrophy (SMA) is an inherited neurodegenerative disease causing motor deficits, from severe infantile muscle weakness with respiratory failure to milder adult onset weakness. SMA leads to motoneuron death and dysfunction (e.g. low firing rates and hyperexcitability) due to maladaptive changes in motoneuron membrane properties from insufficient excitatory sensory inputs. Spinal Cord Stimulation (SCS) targeting sensory afferents might reverse motoneuron dysfunction and enhance motor function in the long term. However, the immediate impact of increased sensory afferent activity from SCS on fine motor control and balance in patients with SMA is uncertain. Here we used data from a pilot study testing SCS efficacy and safety, where 3 ambulatory adults with SMA had epidural leads temporarily implanted near the lumbosacral spinal cord for 4 weeks. Following 3 hour daily sessions combining SCS and exercise, we noted improvements in locomotion, strength, and motoneuron function, persisting even when the stimulation was turned off. To examine SCS effects on complex motor control, participants walked weekly on a progressively narrowing beam with crossed arms and eyes forward, completing 5 trials each with SCSOFF and SCSON. In the first week, participants showed decreased walking distance and increased sway with SCSON, but by week three, their performance matched the SCSOFF condition, with no improvement noted over weeks in the SCSOFF condition. Every week, we found large improvements in performance but not within trials of the same session. This suggests that participants learned to control their limbs during the sessions combining SCS and exercise occurring between each weekly narrowing beam test. Thus, they were able to transfer the learning from less complex tasks like overground walking to a more demanding balance task. To assess changes in motor strategies adopted by the central nervous system (CNS) during SCSON, we compared muscle synergies between conditions and across weeks. Throughout the study, the number and muscle weights of each synergy remained consistent across conditions. In the first week, we detected differences in synergy temporal dynamics between SCSOFF and SCSON that decreased by the end of the study suggesting that the CNS can adapt to the sensory overload from SCS. In summary, we found that

(1) the CNS can integrate SCS without impairing balance and fine motor control. (2) participants learned to control their limbs with SCSON without diminishing the performance with SCSOFF. Importantly, our results show that a potential SCS therapy for SMA participants will not face usability issues due to decreased fine motor control and balance.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.11/I33

Topic: D.08. Multisensory Integration

Support: Canadian Institutes of Health Research
Quebec Pain Research Network
Doggone Foundation
IRCM Foundation

Title: The Neural Basis of Ascending Somatosensory Integration for Control of Movement

Authors: *F. B. BOUROJENI[1], X. ZHANG[2], R. MARTINEZ-GARCIA[3], S. MAHASENAN[1,4], A. A. UPADHYAY[5], V. E. ABRAIRA[6], D. D. GINTY[7], A. KANIA[1]; [1]McGill Univ. / Montreal Clin. Res. Inst. (IRCM), Montreal, QC, Canada; [2]Neural Circuit Develop., McGill Univ. / Montreal Clin. Res. Inst. (IRCM), Montréal, QC, Canada; [3]Harvard Med. Sch., Boston, MA; [4]McGill Univ. / IRCM, Montreal, QC, Canada; [5]Cell Biol. and Neurosci., Rutgers Univ., Piscataway, NJ; [6]Cell Biol. and Neurosci., Rutgers, The State Univ. of New Jersey, warren, NJ; [7]Dept. of Neurosci., Harvard Med. School, Harvard Univ., Boston, MA

Abstract: Rudimentary locomotor behaviors are driven by subcortical circuits. In contrast, a complex and changing environment requires somatosensory integration in the cortex since its disruption results in decreased performance in complex locomotor tasks. However, the identity of the ascending pathways underlying this phenomenon is unclear.
While the lateral spinothalamic tract (STT) has been primarily associated with the relay of noxious and thermal signals to the thalamus, its ventral component, or the vSTT, is proposed to relay crude touch and joint movements in locomoting mammals. Here we demonstrate that the vSTT neurons arising from the V3 spinal cardinal group are the principal source of sensory inputs from the caudal spinal cord to the ventral posterolateral (VPL) thalamus. Anatomical tracing reveals that vSTT neurons receive direct inputs from proprioceptors, Aβ low-threshold mechanoreceptors, and spinal interneurons, as well as from motor brain centers. Combined with their extensive dendritic arborization, these are indicative of somatosensory integration function. Indeed, in vivo juxtacellular recording from vSTT neurons demonstrates that these neurons

readily respond to a wide range of changes in position and directionality of hindlimbs. The principal ascending input to the VPL arise from the dorsal column nuclei (DCN) in the brainstem, however vSTT axons innervate a spatially segregated VPL domain suggesting a functionally distinct pathway to the DCN-VPL, both of which converge onto the S1 cortex. Ablation of vSTT or VPL neurons post-synaptic to them does not alter reflexive or supraspinal responses to noxious or fine touch stimuli in freely moving mice. Instead, such manipulations lead to deficiencies in behaviors associated with the integration of innocuous touch and proprioceptive inputs during movement. Recent functional manipulation of dorsal column nuclei inputs to the VPL implicate it as a somatosensory relay site critical for forelimb motor control. Together, our studies provide evidence for a direct spinothalamic ascending pathway that integrates tactile and proprioceptive inputs and relays them to the thalamus and then the S1 cortex thus facilitating accurate spatiotemporally sensory integration for continual skilled movement.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.12/I34

Topic: E.06. Posture and Gait

Support: NSF DBI 2015317
NSF IIS 2113028
DFG DI 2907/1-1 (Project number 500615768)

Title: Modelling of Contralateral Load and Kinematic Leg Sensory Information in Insect Locomotion

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Abstract: Behaviour relies on the adaptive performance of the motor system, which encompasses lower-level sensorimotor networks. In insects, these networks reside within the ventral nervous system and process sensory information and innervate the muscles, facilitating movement control. Sensory input from limbs, including load information from campaniform sensilla (CS) and kinematic data on joint angles and velocity from the femoral chordotonal organ (fCO), can be received by non-spiking interneurons (NSIs), which adjust muscle activation. Premotor networks generate context-appropriate motor activity for the legs both by using one modality to modulate the gain of another and by integrating sensory information from multiple legs. Electrophysiological studies in Stick Insects have elucidated how NSIs integrate load and

kinematic information to control slow extensor tibiae motor neuron activity. CS presynaptically inhibit fCO afferents, thereby modulating NSI responses. As a result, NSI responses to simultaneous input from both sensory modalities reflect nonlinear summation. In *Drosophila*, a total of 12 leg CS (bCS) project into ipsilateral and contralateral neuromeres, providing direct synaptic input onto tibia flexor motor neurons (MNs). These proximal CS detect increased body load and activate muscle synergies to enhance grip on surfaces. Biomimetic robots have observed maximal strain at this location during stance phase onset, further highlighting the proposed relevance of bilaterally connecting CS for controlling rapid movements. However, how the different afferent pathways from load sensors are utilized to control locomotion remains to be investigated. Utilizing a Synthetic Nervous System (SNS) implemented using the SNS-Toolbox, we propose constructing a neuromechanical model of an insect's posture in its frontal plane, i.e., stabilizing lateral perturbations with a pair of contralateral legs. This system will replicate the described networks, including the integration of load and kinematic feedback from both legs and their effects on synergistically activated muscles. We anticipate that direct pathways from bCS to MNs represent positive feedback to rapidly compensate for external forces, while load information processed by NSIs decreases the gain of kinematically-driven reflexes (e.g., resistance reflexes) to prevent delay-induced instability. The interplay of these sensory modalities should produce highly dynamic responses, e.g., the reflex sign changes during perturbation, ultimately altering muscular output.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.13/I35

Topic: D.04. Interoception

Support: DFG grant Bu857/15

Title: Role of leg-campaniform sensilla in fruit fly adaptive walking

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Abstract: Movement and the perception that an action occurred are essential for behavior and ultimately shape how animals are able to adapt navigation in complex environments. We focus on how an organism's nervous system acquires and integrates sensory information to efficiently react to its environment. For this, we are investigating how specific somatosensory information,

i.e. signals about load, are sent to local nervous centers of *Drosophila melanogaster* (*D.mel*), how this information is processed herein, and what role load sensation plays in the generation of adaptive locomotor behavior. These sensory organs are campaniform sensilla (CS), mechanoreceptors located throughout the fly's exoskeleton. Here, we focus on the function of the 42 sensors located in each leg (Dinges et al. 2020; Pierzchlińska et al. SfN2024). Preliminary results indicate that activation and inhibition of specific leg CS elicit behavioral effects on walking (Dinges, unpubl.). Specific kinematic parameters such as leg swing and stance durations were found to be affected**.** To further dissect this topic, we investigate how increased load reflects on locomotor behavior in the context of CS optogenetic manipulation. For this we use an established approach (Mendes et al. 2014), i.e. adding weight to the fly´s notum - and, while specific CS are optogenetically inhibited, quantify changes in kinematic parameters during walking. We hypothesize that flies with an increased sensory challenge (carrying up to 2x their body weight), while lacking the mode of proprioception encoded by CS, will show behavioral defects due to a lack of locomotor flexibility. Using Split-Gal4 lines to restrict expression to a small subset of leg CS, we show that inhibiting these CS elicits load-dependent kinematic alterations. For example, a line that labels approximately 25% of leg CS shows that the lack of proprioception produces incremental difficulties in walking with increased load. At the most extreme scenario, inhibiting CS while *D.mel* carry 2x their body weight produces up to 20% longer stance amplitudes, as well as stance durations that last up to 25% more time. We believe these results highlight the contribution of proprioception to adaptive walking, as its absence reveals drastic kinematic changes versus internal controls (same fly without optogenetic inhibition), which are proportional to the increase in body load carried (0x, 1x, and 2x). With our approach, we are able to provide evidence on how CS-encoded proprioception functionally contributes to motor control in walking *D.mel*. We also show that these neuronal substrates for a component of proprioception can be reliably targeted and optogenetically manipulated.

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Poster

PSTR467: Posture and Gait Control: Afferent Pathways

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR467.14/I36

Topic: D.04. Interoception

Support: DFG grant CRC1451 (SFB1451/1, project number 431549029)
DFG grant Bu857/15 in the international NeuroNex consortium "C3NS"

Title: Contribution of leg load feedback to walking control in the fruit fly

Authors: *A. PIERZCHLINSKA[1], R. CUSTÓDIO[1], G. F. DINGES[2], E. EHRHARDT[1], T. BOCKEMÜHL[1], J. SEMIONOVA[1], T. STURNER[3,4], G. JEFFERIS[3,4], A. BUSCHGES[1]; [1]Inst. of Zoology, Dept. of Animal Physiol., Univ. of Cologne, Cologne, Germany; [2]Dept. of

Mechanical and Aerospace Engin., West Virginia Univ., Morgantown, WV; [3]Neurobio. Div., MRC Lab. of Mol. Biol., Cambridge, United Kingdom; [4]Drosophila Connectomics Group, Department of Zoology, University of Cambridge, Cambridge, United Kingdom

Abstract: Walking is an important mode of locomotion for terrestrial animals, including insects. The fruit fly, *Drosophila melanogaster*, is a convenient model to study the neural control of walking, considering its versatile locomotor behaviour, numerically simple central nervous system and the available neurogenetic tools. Here, we studied the role of sensory feedback signals from the leg, specifically load feedback, provided by 42 campaniform sensilla (CS, Dinges et al. 2021) for generating leg stepping and motor flexibility, i.e. controlling walking speed. CS detect changes in load and convey this information to neural circuits in the ventral nerve cord (VNC, Harris et al. 2020, 2022), the invertebrate equivalent of the spinal cord. In other insects, load feedback is known to influence leg stepping motor output, kinematics and interleg coordination (Bidaye et al. 2018). However, there is limited information about this sensory system in the fruit fly (Tsubouchi et al. 2017). To solve this issue, we traced CS neurons in the VNCs and legs of the same flies, using a stochastic labelling method (Multi Color Flip-Out - MCFO, Nern et al. 2015). We discovered that in most cases the CS neurons show unilateral arborisation patterns within a single leg-related neuropil. Moreover, individual arborisation patterns seem to be associated with CS location on the leg. However, for a few CS we noticed unique arborisation patterns, possibly correlated with a distinct function of those CS. Finally, we used the fly Male Adult Nerve Cord (MANC) connectome (Takemura et al. 2023, Marin et al. 2023, Cheong et al. 2023) to predict local connectivity of some of the neurons found in our experiments. In order to analyse the role of CS in the walking generation, we performed behavioural experiments in freely-walking flies while optogenetically inhibiting subsets of the 42 CS. Silencing up to 25% of CS affected frequency of walking behaviour, length of walking bouts and speed distribution. Depending on the subset, the results differed in the strength of the inhibitory effect, suggesting heterogeneity in the role of walking control among CS. These combined approaches will help us to understand the details of CS function in control of walking.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.01/Web Only

Topic: E.08. Respiratory Regulation

Support: 5K08NS112573
5R01DC004290

Title: Radiofrequency ablation of a focal site in the human amygdala affects apnea susceptibility: a potential treatment for Sudden Unexpected Death in Epilepsy

Authors: *A. E. RHONE[1], M. MOWLA[1], S. KUMAR[1], C. K. KOVACH[1], A. C. CHAN[2], J. I. BERGER[1], C. M. GARCIA[1], H. KAWASAKI[1], M. A. HOWARD III[1], B. J. DLOUHY[1]; [1]Neurosurg., Univ. of Iowa, Iowa City, IA; [2]Psychiatry, Univ. of Iowa, Coralville, IA

Abstract: We have previously identified a site in the human amygdala that inhibits respiration when electrical stimulation is delivered or when seizures spread to that area [Rhone et al. 2020, Harmata et al. 2023, JCI-Insight], which we termed the "amygdala inhibition of respiration" (AIR) site. Crucially, patients were unaware that they stopped breathing and showed no signs of panic or alarm. We hypothesized that this site may be key to understanding Sudden Unexpected Death in Epilepsy (SUDEP). Radio frequency thermocoagulation (RFTC) of brain tissue is emerging as a useful tool for the management of medically refractory focal epilepsy. In RFTC, clinicians create a lesion at the seizure onset zone using radiofrequency electrical current delivered in a bipolar fashion. RFTC can be delivered in a standard hospital room, takes minutes, and is well tolerated and safe [Catenoix et al. 2018, Epilepsy Res]. Because the procedure occurs during chronic seizure monitoring with implanted electrodes, it affords a unique opportunity to examine neural responses before and after focal thermocoagulation. Mesial temporal lobe structures, such as the amygdala, are commonly epileptogenic and can be targeted by RFTC for diagnostic, and potentially therapeutic, purposes. We tested the hypothesis that a clinically-indicated lesion of the AIR site using RTFC would reduce apnea susceptibility.We evaluated neural responses, respiratory physiology, and behavior before and after RFTC of the mesial temporal lobe in patients undergoing intracranial electroencephalographic (iEEG) monitoring for seizure localization. Thermocoagulation of the intended structures was confirmed using post-procedure MRI. Electrical stimulation functional mapping and cortico-cortical evoked potentials (CCEPs) were recorded before and after RFTC. Respiratory measures at rest and during electrical stimulation mapping were obtained along with iEEG before and after RFTC. Mood and dyspnea ratings were also obtained. We found that the focal RFTC lesion of the AIR site prevented stimulation-induced apnea. Ratings of mood and dyspnea were generally unaffected. Amplitude of CCEPs elicited by stimulation at the ablated site were reduced following RFTC, but similar pre/post RFTC at nearby sites. In one patient, spontaneous seizures pre-RFTC were compared to seizures after RFTC of the AIR site. Before the RFTC, spontaneous and electrical-stimulation-evoked seizures resulted in apnea requiring clinical intervention. After RFTC, no apnea was observed. Findings suggest that focal lesions to the AIR site prevent seizure and stimulation-induced apneas and may provide a therapeutic target for SUDEP prevention.

Disclosures: A.E. Rhone: None. **M. Mowla:** None. **S. Kumar:** None. **C.K. Kovach:** None. **A.C. Chan:** None. **J.I. Berger:** None. **C.M. Garcia:** None. **H. Kawasaki:** None. **M.A. Howard:** None. **B.J. Dlouhy:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.02/I37

Topic: E.08. Respiratory Regulation

Support: NINDS K08 NS112573 01

Title: Changes in respiration entrained brain-regions during awake, sleep, anesthetized, and ventilated states

Authors: *M. MOWLA[1], A. E. RHONE[1], S. KUMAR[1], C. K. KOVACH[1], G. B. RICHERSON[2], J. A. WEMMIE[3], A. C. CHAN[4], H. KAWASAKI[5], M. A. HOWARD III[6], B. J. DLOUHY[1];
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Abstract: Our understanding of the forebrain control of respiration in humans is limited. Many tasks during our day-to-day activities require modulation of respiration, and the forebrain plays a crucial role in coordinating this modulation by sending signals to the brainstem respiratory oscillator. To unveil the mechanistic basis of forebrain control, we studied how breathing is represented in different brain regions during responsive states (awake) and unresponsive states (sleep, anesthesia, and breathing with ventilator support). We recorded respiration signals and local field potentials (LFPs) simultaneously from eight human patients with intractable epilepsy undergoing intracranial EEG for seizure focus localization. Recordings were made in the operating room while the patients were (i) spontaneous breathing in the awake state, (ii) spontaneous breathing under anesthesia, (iii) breathing with ventilator support (iv) spontaneous breathing during sleep, (v) ventilator support with high tidal volume, (vi) ventilator-induced apnea. After preprocessing the data, we computed the coherence between the respiration signal and LFPs at the breathing frequency. Group level inference was performed using a linear mixed-effect model to examine the state-dependent changes in respiratory entrainment in each brain region. Our analysis showed that multiple brain regions entrain to respiration in all states. State specific changes in entrainment to respiration were also observed. More specifically, temporal regions were entrained during the awake state, the amygdala and hippocampus entrained during sleep, and parietal regions entrained during anesthetized states. The postcentral gyrus, fusiform gyrus, insula, and parietal regions showed significant changes in respiratory entrainment in different states. In conclusion, our data show a wide range of forebrain responses to breathing which is modulated by arousal state (awake/sleep/anesthesia). However, the behavioral, perceptual, and emotional consequences of state-dependent changes in respiratory entrainment need to be investigated further.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.03/I38

Topic: E.08. Respiratory Regulation

Support: NINDS K08 NS112573 01

Title: Exploration of the role of thalamus in respiration using electrical stimulation and intracranial recordings in humans

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Abstract: The role of thalamus as a ‘gateway’ for sensory signals from the external world to cortex is well known. However, the role of thalamus in processing visceral signals, such as respiration, is not understood. Although a few studies in animals have shown that thalamus represents state of respiration [Chen et al, 1992, PMID: 1455102], evidence for relation between respiration and thalamic activity in humans remains scarce. Toward this aim, we recorded local field potentials (LFPs) from and electrically stimulated the thalamus in human patients with intractable epilepsy undergoing intracranial EEG for seizure focus localization. We recorded LFPs in 5 patients who had thalamic electrodes placed as part of their clinical care plan. Recordings were made at bedside or in the operating room while subjects were (i)breathing spontaneously in awake state (ii)breathing spontaneously without ventilator support in general anesthesia induced unresponsive state and (iii)breathing with ventilator support in anesthetized and paralyzed state. Data analysis was performed at each contact separately calculating power spectral density, coherence between the respiration and LFP. Several sites located in the anterior and posterior thalamus showed strong coherence with spontaneous respiration in awake and anesthetized states. When breathing with ventilator support, only posterior, and not anterior, sites located in the ventro-posterior lateral nucleus (VPL) showed strong coupling with breathing.Electrical stimulation (bipolar, biphasic, 1.5-3.5mA, 50Hz) of thalamus in 2 patients resulted in apnea lasting the duration of stimulation. Stimulation with higher current (3.5mA) led to apnea persisting after stimulation offset. Anatomical parcellation of the thalamus localized apneic sites to the ventral anterior (VA) nucleus. Stimulation of posterior thalamic sites showed no apnea. Our data suggests that rhythm of spontaneous respiration, both under the awake and unresponsive state is represented in the thalamus. Differential coupling of thalamic sites to respiration along the anterior-posterior axis during spontaneous and ventilator supported breathing suggest that posterior sites may be more engaged in representing the bottom-up sensory effects (e.g., of lung contractions) of respiration. Following our previous work [Dlouhy et al, 2015, PMID: 26180203; Rhone et al, 2020; PMID: 32163374] identifying apneic sites in the amygdala, we have electrically stimulated numerous sites in the brain to test their relation to respiration. In our observations, the thalamus is the only area other than amygdala which can inhibit respiration following electrical stimulation.

Disclosures: S. Kumar: None. **A.E. Rhone:** None. **C.K. Kovach:** None. **M. Mowla:** None. **J.I. Berger:** None. **A.C. Chan:** None. **J.A. Wemmie:** None. **G.B. Richerson:** None. **B.J. Dlouhy:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.04/I39

Topic: E.08. Respiratory Regulation

Support: NIH R01 HL161582
NSF DMS-2052109
NIH RF1 NS118606-01

Title: Asymmetric neuromodulation in the respiratory network contributes to rhythm generation

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Abstract: Like other brain circuits, the brainstem respiratory network is continually modulated by neurotransmitters that activate slow metabotropic receptors. In many cases, activation of these receptors only subtly modulates the respiratory motor pattern. However, activation of some receptor types evokes the arrest of the respiratory motor pattern as can occur following the activation of μ-opioid receptors. We propose that the varied effects of neuromodulation of the respiratory network depend on the pattern of neuromodulator receptor expression and their effect on the activity of their post-synaptic targets. Because a comprehensive characterization of these cellular properties across the respiratory network remains challenging, we test our hypothesis by combining computational modelling with ensemble electrophysiologic recording in the pre-Bötzinger Complex (pre-BötC) using high-density multi-electrode arrays (MEA). We first developed a computational model of the respiratory network which encapsulates the hypothesis that neuromodulatory transmission is organized asymmetrically across the network to drive rhythm generation. Then, we compared the model predictions of increasing the strength of neuromodulatory connections based on their net effect on post-synaptic targets with ensemble recordings of respiratory network activity of the pre-BötC before and after systemic administration of neuromodulatory receptor agonists. Increasing slow inhibition in the model predicted a slight increase in respiratory frequency without changing the distribution of neuronal activities generated by the network, which we confirmed in experiments examining the effect of systemic administration of the 5HT1aR agonist 8-OH-DPAT. Increasing slow excitation in the model predicted a collapse of respiratory network activity associated with a significant reduction in the number of active neurons sparing a subset with tonic or bursting activities. These

predictions were confirmed in experiments examining pre-BötC ensemble activities before and after systemic administration of the μ-opioid receptor agonist fentanyl. We conclude that asymmetric neuromodulation contributes to respiratory pattern generation and accounts for its varied effects on breathing.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.05/I40

Topic: E.08. Respiratory Regulation

Support: R21 HD110951-01
HL155721
HD110951
NS110169

Title: Syncytial Oscillations Along the Ventral Respiratory Column May Enhance the Robustness of Respiratory Rhythmogenic Networks

Authors: B. GOURÉVITCH[1], T. PITTS[2], K. E. ICEMAN[3], N. TOPORIKOVA[4], ***N. MELLEN**[5];
[1]Dept. Cognition & Behavior, Inst. Pasteur, Paris, France; [2]Speech Language and Hearing Sci., Univ. of Missouri, Columbia, Columbia, MO; [3]Neurolog. Surgery, Univ. of Missouri, Columbia, Valparaiso, IN; [4]Biol., Washington and Lee Univ., Lexington, VA; [5]Univ. of Louisville, Louisville, KY

Abstract: Networks that control and generate breathing are distributed along the ventral respiratory column (VRC) in ventrolateral medulla. These phenotypically heterogeneous networks are exposed at the surface of the sagittally-sectioned rodent hindbrain preparation (SSRH) isolated from neonate (P0-P4) pups. In transgenic mice expressing the genetically encoded Ca^{2+} indicator GCaMP6F in the germline, these networks can be recorded from optically. In a recent study using these methods, stationary, low-amplitude oscillations tightly synchronized along the VRC were detected following synaptic blockade. These oscillations are attenuated or eliminated using gap-junction blockers and were detected in both neurons and glia. In this study, we characterize features of this syncytial oscillation. The observation that the syncytial rhythm is unaffected by stimulus trains applied to neurons within the syncytium suggests that the rhythmogenic mechanism is not voltage dependent. A plausible candidate mechanism is ryanodine receptor-mediated release of Ca^{2+} from intracellular stores, which might account for synchronous oscillations along the VRC via paracrine diffusion of IP_3 through gap junctions. Consistent with this conjecture, syncytial oscillation amplitude increased following

bath application of caffeine or thyrotropin-releasing hormone (TRH), which upregulate IP_3-mediated release from intracellular stores. A possible functional role for this oscillatory syncytium is that it may increase the robustness of respiration by providing a mechanism for reinitiating respiratory rhythm. To test this conjecture, we monitored recovery of opioid-induced silencing of respiratory network activity. We found that following prolonged apnea induced by bath application of the opioid agonist [D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin (DAMGO; 1 µm), respiratory rhythm eventually resumed following DAMGO wash-out with aCSF. A consistent feature of this recovery was the early emergence of the fast, low-amplitude, synchronous syncytial oscillation along the VRC, followed by the gradual appearance of sparse inspiratory bursts phase-locked to syncytial oscillations. Once respiratory rhythm returned to control frequency, syncytial oscillations were no longer detectable. These findings suggest that the syncytial oscillations along the VRC may provide a mechanism for restoration of respiratory rhythm following disruption.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.06/J1

Topic: E.08. Respiratory Regulation

Support: Fritz-Thyssen-Stiftung (grant # 10.20.1.004MN)
Deutsche Forschungsgemeinschaft (grant # 450241946)

Title: Genetic identification of medullary neurons underlying congenital hypoventilation

Authors: *K. CUI[1], Y. XIA[2], L. R. HERNANDEZ-MIRANDA[3];
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Abstract: Hypoventilation disorders originate from genetic or environmental factors, yet the specific neural populations and circuits affected in these disorders are poorly understood. Here, we show that dysfunction of previously unidentified medullary neurons co-expressing Lbx1 and Phox2b (dB2 neurons) underlie congenital central hypoventilation. dB2 neurons belong to a small medullary neuron type that emerge from rhombomeres 2 to 6. This defined neuron type is characterized by the co- expression of Lbx1 and Phox2b during development. In our talk, we will present data illustrating that a specific subgroup of dB2 neurons (generated from rhombomere 5) is crucial for regulating the hypercarbic reflex and respiratory frequency in neonates. In addition, we will show that other dB2 neurons subgroups (generated from rhombomere 6) are essential for regulating respiratory tidal volumes, as well as for the maintenance of respiratory stability and

survival in neonates. Our studies thus provide new insights into the functional significance of dB2 neurons in neonatal respiratory physiology, and their relevance in congenital hypoventilation disorders.

Disclosures: K. Cui: None. **Y. Xia:** None. **L.R. Hernandez-Miranda:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Program #/Poster #: PSTR468.07/J2

Topic: E.08. Respiratory Regulation

Support: Fritz-Thyssen-Stiftung (grant no. 10.20.1.004MN)
Deutsche Forschungsgemeinschaft (grant no. 450241946)
Deutsche Forschungsgemeinschaft (grant no. 514060831)

Title: Impairment of dB2 neurons causes congenital hypoventilation

Authors: K. CUI[1], Y. XIA[2], ***L. R. HERNANDEZ-MIRANDA**[3];
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Abstract: Mutations in the transcription factors *PHOX2B* or *LBX1* correlate with congenital hypoventilation, a condition characterized by alveolar hypoventilation, central apnea and diminished chemoreflexes, particularly to abnormal high levels of arterial PCO_2. The dysfunctional neurons causing this respiratory disease are largely unknown. Here, we show that distinct sets of medullary neurons co-expressing both transcription factors (dB2 neurons) account for specific phenotypes seen in congenital hypoventilation. Our data show that these neurons are key in i) respiratory tidal volumes, ii) the hypercarbic reflex, iii) neonatal respiratory stability, and iv) neonatal survival. Our data thus provide functional evidence for the critical role of medullary dB2 neurons in neonatal respiratory physiology. In summary, our work identifies subgroups of dB2 neurons regulating neonatal breathing homeostasis, dysfunction of which causes congenital hypoventilation.

Disclosures: K. Cui: None. **Y. Xia:** None. **L.R. Hernandez-Miranda:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.08/J3

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01HL163578

Title: Intracranial Responses to Respiratory Challenges in Sensorimotor and Insular cortices are modulated by the Strength and the Perception of the Challenge

Authors: *J. HERRERO RUBIO[1], S. BICKEL[2], T. SIMILOWSKI[3], N. MESGARANI[4], A. D. MEHTA[5];
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Abstract: Although advancements in the field of interoception have been made over the past few years, the neural correlates of interoceptive processes are still elusive. We adapted a recently developed respiratory task (Respiratory Resistance Sensitivity Task) to precisely quantify the way the brain processes ascending respiratory signals. In this task, the airways are partially obstructed during the inspiratory cycle by a filter (inspiratory loading). Ten epilepsy patients implanted with intracranial electrodes (iEEG) in cortical and subcortical areas completed this task, detecting loads of different magnitudes (weak/subthreshold vs. strong/suprathreshold) while breathing through a mouthpiece. Our results revealed new insights into the brain's response to respiratory challenges. Compared to (non-loaded) control, loaded inhalations showed a decrease in airflow and an increase in mouth-pressure, as expected. At the neural level, loaded inhalations showed increased high frequency activity (HFA, 70-150hz) in the sensorimotor, insular, and frontal (orbitofrontal, rostro-medial, anterior cingulate) cortices. This effect was proportional to the load magnitude, with larger loads eliciting higher HFA compared to smaller loads. At the behavioral level, loads that were consciously perceived by the subjects elicited higher HFA than those that were not (missed). In addition, when the subjects breathed harder in reaction to a given load (e.g., compensatory mechanism), the coherence between the sensory and motor cortex in the beta band (15-30hz) was enhanced. These results reveal 1) the key cortical areas contributing to the detection of respiratory sensations, 2) the neuronal “gain” mechanisms underlying the processing of loads of different magnitudes (subthreshold vs. suprathreshold), and 3) the respiratory-motor compensatory strategies that are necessary at the cortical level to not only detect a load but to react to meet the ventilatory challenge of the load (e.g., restore homeostasis). These observations are the first intracranial reports of respiratory challenges in humans and offer an insight into the neural mechanisms of breathing interoception and breathing pathology to better understand the abnormal neural processing or respiratory sensations in those living with persistent breathlessness (i.e., dyspnea, COPD, chronic anxiety).

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Program #/Poster #: PSTR468.09/J4

Topic: E.08. Respiratory Regulation

Support: NIH (R01 HL128970, R01 HL133100, and R01 HL138932)
AHA (24CDA1270910)

Title: Targeting melanocortin 4 receptor to treat sleep-disordered breathing

Authors: *M. R. AMORIM[1], O. AUNG[2], F. ANOKYE-DANSO[3], J. DE DEUS[1], N. WILLIAMS[1], J. XIONG[4], O. DERGACHEVA[1], S. B. FONTI[1], M. WU[4], R. S. AHIMA[3], D. S. MENDELOWITZ[1], V. POLOTSKY[1];
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Abstract: There is no effective pharmacotherapy for sleep disordered breathing (SDB). A melanocortin receptor 4 (MCR4) agonist, setmelanotide (SET), is used to treat genetic obesity caused by abnormal melanocortin and leptin signaling. We hypothesized that SET can treat SDB in diet induced obese mice. We performed a proof-of-concept randomized crossover trial of a single dose of SET *vs* vehicle and a two-week daily SET vs vehicle trial in obese mice. We also examined co-localization of *Mcr4* mRNAs with a marker of CO_2 sensing neurons PHOX2b in the brainstem and performed chemogenetic studies expressing *Cre*-dependent designer receptors exclusively activated by designer drugs (DREADD) in *Mcr4-Cre* mice. SET increased minute ventilation across sleep/wake states, greatly enhanced the hypercapnic ventilatory response (HCVR) and abolished apneas during sleep. PHOX2b+ neurons in the nucleus of the solitary tract (NTS) and the parafacial region expressed *Mc4r*. Chemogenetic stimulation of the MC4R+ neurons in the parafacial region, but not in the NTS, augmented the HCVR without any changes in metabolism. Parafacial MC4R neurons projected to the respiratory pre-motor neurons expressing cholera toxin B after C3-C4 spinal cord injections. In conclusion, MC4R agonists enhance the HCVR and treat SDB by acting on the parafacial MC4R+ neurons.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.10/J5

Topic: E.08. Respiratory Regulation

Support: NIH NHLBI HL146477-04
University of Minnesota Division of Physical Therapy

Title: Androgen Receptor Antagonism Inhibits Expression of Phrenic Long-Term Facilitation in Male Rats

Authors: A. DUNLAP-SMITH, E. JUAREZ LOPEZ, *B. DOUGHERTY;
Univ. of Minnesota - Twin Cities, MINNEAPOLIS, MN

Abstract: Female rats require circulating estrogen to express spinal neuroplasticity. For example, acute intermittent hypoxia (AIH) induces a progressive elevation in phrenic neural output; a form of respiratory neuroplasticity termed long-term facilitation (pLTF). Females only express AIH-induced pLTF during periods of the estrous cycle (similar to the human menstrual cycle) with high levels of circulating estrogen. Removal of the ovaries, the primary source of circulating estrogen, also impedes pLTF for several weeks. The role of sex hormones in male pLTF expression is less understood. Testosterone is the principal circulating sex hormone in males. pLTF declines in aging male rats (correlating with decreasing testosterone levels), and castration (removing the primary source of circulating testosterone) abolishes pLTF, suggesting that testosterone may be necessary to permit respiratory neuroplasticity. Further, testosterone acts through androgen receptors (AR), and ARs are expressed on phrenic motor neurons in the ventral cervical spinal cord. However, testosterone is also converted to estrogen in the CNS, complicating our mechanistic understanding. In fact, conversion of testosterone to estrogen is needed to restore pLTF in castrated male rats when exogenous testosterone is supplemented, implicating estrogen receptors (not ARs) for pLTF. Accordingly, we hypothesized that AR activation would *not* be necessary for the development of pLTF in gonadally-intact, young-adult male rats. We performed *in vivo* phrenic nerve recording studies in 2-3 month old male Sprague-Dawley rats (n = 13). Rats received either Enzalutamide (AR antagonist; 10 mg/kg; i.p.) or vehicle control 2-3 hours prior to AIH. Phrenic nerve amplitudes were quantified in anesthetized, mechanically ventilated rats for a baseline period, during AIH, and for 60 min thereafter to assess for pLTF expression. The placebo group demonstrated a statistically significant increase in phrenic amplitude at 60 min post-AIH consistent with pLTF (2-way RMANOVA and Bonferroni *post-hoc* analysis) relative to both Time Controls (p=0.042) and Enzalutamide treated rats (p=0.049). These results indicate that AR antagonism in young-adult, gonadally-intact male rats significantly impacts the expression of pLTF and suggests that AR activation is necessary for AIH-induced pLTF. Understanding the influence of testosterone on AIH-induced neuroplasticity is important for optimizing AIH as a potential therapeutic intervention for patients with spinal cord injury, which disrupts naturally circulating sex hormones.

Disclosures: A. Dunlap-Smith: None. **E. Juarez Lopez:** None. **B. Dougherty:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.11/J6

Topic: E.08. Respiratory Regulation

Support: National Heart Lungs Brain Institute R01HL146477
Rehabilitation Science Graduate Program, UMN Medical School

Title: Characterization of G-protein estrogen receptor expression in phrenic motor neurons in male and female rats.

Authors: *J. M. L. GRITTNER[1], A. DAVIS[2], E. J[2], B. J. DOUGHERTY[3];
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Abstract: Estrogen signaling is necessary for respiratory neuroplasticity in female and male rats, but the estrogen receptor(s) that mediate this function are undefined. The three known estrogen receptor subtypes (ERα, Erβ, and the G-protein coupled estrogen receptor [GPER]) are all expressed in brainstem respiratory centers, and prior studies demonstrated that ERα and ERβ are present in spinal phrenic motor neurons. However, the expression of GPER has yet to be characterized in the phrenic motor nucleus. We hypothesized that: (1) GPER would be expressed in retrogradely identified phrenic motor neurons of both male and female rats, (2) females would express higher levels of GPER than males, and (3) GPER expression in females would be influenced by estrus cycle stage with peak expression occurring during diestrus. Detailed co-localization studies using immunohistochemistry (IHC) were completed in 2–3 month-old Sprague-Dawley rats. Analysis of mean fluorescence intensity showed the clear presence of GPER in retrogradely identified phrenic motor neurons ($p>0.0001$). Contrary to our hypothesis, our data indicated similar GPER expression between sexes ($p = 0.273$). To assess whether GPER expression was impacted by estrous cycle stage in female rats, we again compared GPER mean florescence intensity in retrogradely identified phrenic motor neurons from females in the proestrus (high levels of circulating E2) or diestrus (low circulating E2) stage of the estrus cycle. Our data showed higher GPER expression during the diestrus stage than the proestrus stage ($p = 0.008$). This apparent inverse relationship in GPER expression relative to circulating estrogen in phrenic motor neurons is consistent with findings from other CNS regions. Collectively, our data identify GPER in phrenic motor neurons of male and female rats and show evidence that expression levels fluctuate relative to circulating estrogen.

Disclosures: J.M.L. Grittner: None. **A. Davis:** None. **E. J:** None. **B.J. Dougherty:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

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Program #/Poster #: PSTR468.12/J7

Topic: E.08. Respiratory Regulation

Title: Medullary serotonergic neurons with a high degree of intrinsic pH chemosensitivity drive firing of retrotrapezoid neurons in response to acidosis.

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[1]Neurol., Univ. of Iowa, Iowa City, IA; [2]Univ. of Iowa, Iowa City, IA

Abstract: Rationale: Serotonergic (5-HT) neurons of the medullary raphe and Phox2b expressing neurons of the retrotrapezoid nucleus (RTN) are two candidates for central CO_2 chemoreceptors. However, their relative contribution to respiratory chemoreception is unknown. We previously demonstrated that the CO_2 response of RTN neurons is dependent on 5-HT_7 receptors (Wu et al, J Physiol, 2019). Here we compared intrinsic chemosensitivity of RTN and 5-HT neurons. We then used optogenetics to determine whether 5-HT neurons stimulate RTN neurons in response to an increase in CO_2. Methods: The midline medulla was dissected from P10-P18 *ePet*-EYFP mice. Tissue was enzymatically digested and plated onto glass coverslips. Cells were allowed to attach to the substrate for 2-3 hours. Patch clamp recordings were then made from YFP neurons after 1-2 days. The same methods were used for RTN neurons except that dissections were made from the ventrolateral medulla of P7-P8 Phox2b-Cre::Floxed tdTomato::ChAT-GFP mice, and recordings were made from Phox2b+/ChAT- neurons 1-2 days later. In a separate set of experiments RTN neurons were acutely dissociated as above, and co-plated with midline medullary neurons from mice expressing channelrhodopsin (ChR) in serotonergic (TPH2) neurons (JAX 014555). Recordings were made from RTN neurons after 17-69 days. Results: In response to an increase in CO_2 from 5% to 9% (pH 7.4 to 7.2), 65 of 118 Pet1+ neurons (55%) increased their firing rate by more than 20%, with an average response to 255% of control (121-1268%). In contrast, 18 of 74 RTN neurons (24%) increased their firing rate by more than 20%, with an average response to 158% of control (121-215%). Neurons that expressed Neuromedin B (RNAScope) were not more likely to be chemosensitive. When recordings were made from RTN neurons co-plated with 5-HT neurons expressing ChR, responses to both CO_2 and laser light (5 Hz) were measured from 61 RTN neurons. Of these, 48 of 61 (79%) RTN neurons increased their firing rate to more than 120% of control (mean 561%) with those neurons having a large response to CO_2 also having a large response to laser light ($p<0.0001$). Conclusions: Serotonergic neurons are more likely than RTN neurons to have a high degree of intrinsic (cell-autonomous) chemosensitivity, and their responses are significantly larger. If RTN and 5-HT neurons are maintained in vitro for long enough to re-form synaptic connections, RTN neurons develop a 5-HT dependent CO_2 response. These results indicate that RTN neurons may play an important role in the system level response to CO_2 by relaying the pH response of 5-HT neurons to the respiratory network, but play less of a role as chemoreceptors themselves.

Disclosures: G.B. Richerson: None. **E. Bravo:** None. **Y. Wu:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.13/J8

Topic: E.08. Respiratory Regulation

Support: KAKENHI 22H05557
JSPS Fellows 23KJ0245
Japan Foundation for Applied Enzymology Research Grant

Title: Spatio-temporal dynamics of the neural circuits generating eupnea and ventilatory responses

Authors: *M. OKAZAKI, T. KOGANEZAWA;
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Abstract: Respiration is rhythmic and flexible depending on external and internal conditions, such as hypoxia and emotion. The neural circuits in the respiratory center generate various respiratory patterns, and they should be dynamically altered as respiration changes. Since the circuits are composed of various neurons located widely in the respiratory center, the simultaneous recording of a large number of respiratory neurons is necessary to understand the neural circuits generating respiration. In this study, we aimed to detect the spatio-temporal population dynamics among the respiratory center generating eupnea and ventilatory responses. We performed the *in situ* arterially perfused preparation of male rats and placed a high-density neural probe, Neuropixels 1.0, in the respiratory column of the medulla. After aligning the neural activities by the respiratory phases, the principal component analysis was applied to characterize neural populations of recorded neurons. When eupnea was observed, the temporal dynamics of the neural population according to respiratory phases and the location of contributing neurons were identified. When the ventilatory response to the acute hypoxia was observed, the neural population dynamics altered. We identified the changes in the activities of neurons that led to this alteration and the location of those neurons. These findings demonstrated the alteration of the neural circuits underlying the different respiratory patterns.

Disclosures: M. Okazaki: None. **T. Koganezawa:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: NIH/NIDA R01-DA057767
NIH/HLBI R01-HL163965

Title: Noradrenergic neuromodulation of glutamatergic synaptic drive in the preBötzinger Complex

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Abstract: Rhythmic neural network activity from the preBötzinger complex (preBötC) underlies inspiratory rhythms to sustain mammalian life. Insights gained through both experimental and computational approaches based on the isolated preBötC have suggested that subtle changes in intrinsic and synaptic properties can have a profound impact on mechanisms underlying the emergence of network activity. While neuromodulators, such as norepinephrine (NE), are recognized for their role in orchestrating stability and flexibility of rhythmogenesis, much of our understanding for the basis by which neuromodulation acts in the preBötC is largely restricted to the level of individual neurons. For example, while NE has been shown to induce conditional intrinsic bursting dependent on Ca^{2+}-activated nonselective cation currents (ICAN) among preBötC neurons, how NE affects synaptic properties in the preBötC remains largely undefined. Here, we address this paucity in knowledge by characterizing the impact of NE neuromodulation in the synaptically connected inspiratory network. We found that NE-mediated action recruits NMDAR to stably enhance preBötC network burst amplitude ($P=0.0018$) and modulate frequency ($P<0.0001$; $n=29$). Recruitment of NMDAR enhances inspiratory drive potentials and currents (IDP $P=0.0305$ / IDC $P=0.0219$; $n=5$) independent of changes to AMPAR-mediated drive. In contrast, experimental data supported by computational modeling suggests that blocking ICAN with FFA has mixed effects on network amplitude and frequency. Our computational studies indicate these mixed effects depends on whether the source of intracellular Ca2+ is elevated via synaptic mechanisms (e.g., NMDAR) or VGCC). Our study reveals NE signaling alters the state of preBötC network behavior via NMDAR activation, a synaptic mechanism whose contribution to preBötC activity has largely been discounted. Our data also indicates that synaptic NMDAR activity serves as an unexpected potential source of synaptic calcium that may facilitate network synchrony as posited by Phillips et al. (2019). This study reveals enhanced adrenergic tone changes respiratory network behavior via modulation of both intrinsic and synaptic mechanisms and reveals a previously unappreciated but important role of NMDAR activity in neuromodulation of the inspiratory network.

Disclosures: A.K. Tryba: None. **J. Viemari:** None. **Y. Wang:** None. **A.J. Garcia:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: JSPS KAKENHI 18H02722
JSPS KAKENHI 21H02816
JSPS KAKENHI 20K09207

Title: Synaptic connections between the Central Amygdala and the preBötzinger complex: a biophysical basis for emotional and pathological modulation of breathing

Authors: J. GU[1,2], Y. K. SUGIMURA[3], Y. TAKAHASHI[4], F. KATO[5], *C. A. DEL NEGRO[6];
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Abstract: Breathing is a critical behavior essential for life. While breathing is often automatic, occurring continuously without thought, it is constantly adapting to environmental stimuli and physiological needs. The perception of emotion is one of many factors that can influence breathing pattern, but the underlying mechanism remains unclear. A plethora of polysynaptic pathways may exist between regions of the brain associated with emotion, including the prefrontal cortex and limbic system, and respiratory sites of the medulla. However, we demonstrate a direct relationship between two indispensable sites: the central amygdala (CeA), a major output hub of the Amygdala, and the brainstem preBötzinger complex (preBötC), which generates the fundamental rhythm and pattern for breathing. The connection is monosynaptic and inhibitory, involving GABAergic CeA neurons whose axonal projections form synapses on respiratory neurons in the preBötC and act predominantly via ionotropic $GABA_A$ receptors to produce inhibitory postsynaptic currents. This pathway provides a mechanism for emotional or painful stimuli to arrest breathing. Moreover, the CeA-to-preBötC projection may help explain respiratory-related pathologies, such as sudden unexpected death in epilepsy, a fatality attributable to long-last apneas that follow seizures which invade the amygdala. The CeA-to-preBötC link may be involved in more mild anxiety-related conditions, which incorporate bradypnea or short apneas, or even panic. These results elucidate a link between emotions and breathing, both of which constitute key brain functions in humans and all mammals.

Disclosures: J. Gu: None. **Y.K. Sugimura:** None. **Y. Takahashi:** None. **F. Kato:** None. **C.A. Del Negro:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.16/J11

Topic: E.08. Respiratory Regulation

Title: A genetically-encoded nuclear calcium sensor for imaging the activity of preBötzinger complex neurons

Authors: *M. K. STETTLER[1,2], A. SIEGL[2], J. C. REKLING[2];
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Abstract: The preBötzinger complex (preBötC) of the lower medulla generates the rhythm underlying inspiratory breathing movements in mammals. Tissue slices taken from the medulla of mice that capture the preBötC generate a respiratory-like rhythm for weeks when cultured. We drop-transduced these organotypic slice cultures with a virus expressing a histone-associated genetically-encoded calcium sensor - AAV-Syn-H2B-jGCaMP8m-WPRE (AAV9) - one day after they were put in culture. Seven to 14 days later, we observed rhythmic nuclear calcium transients in hundreds of preBötC neurons simultaneously using wide-field fluorescent imaging. Because the sensor is confined to the nucleus, neurons are easily distinguished, in contrast to soma-filling sensors. We found that the vast majority of calcium transients were within a hundred milliseconds of network-wide bursts. We found a spatially distinct core and periphery to the preBötC; in neurons of the core, both the raw and normalized amplitude of calcium transients is greater than in neurons of the periphery. Moreover, the timing of calcium transients in neurons of the core is significantly less variable burst-to-burst. We applied the μ-opioid receptor agonist DAMGO (1-5 μM) to slice cultures and found that the frequency of rhythmic preBötC events decreased and that the decrease was not due to neurons of the core or periphery dropping out of the rhythm, but may instead reflect a change in network dynamics. The use of genetically-encoded calcium sensors confined to the nucleus may aid in delineating changes in preBötC network dynamics at a single-cell resolution, and cyclic changes in nuclear calcium should be included in future models of rhythmicity.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: R01 HL1660317
R00 HL145004

Title: Modulating breathing: mapping inhibitory and excitatory projections to the preBotzinger complex

Authors: *E. REILLY[1], J. ARTHURS[1], G. LOGINOV[1], N. A. BAERTSCH[1,2,3];
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Abstract: Breathing relies on rhythmic activity generated by the preBotzinger complex (preBotC), a small brainstem region. Because breathing is influenced by many different physiological, behavioral, and emotional contexts, the preBotC is not only highly connected with nearby respiratory-related regions in the hindbrain, but also has widespread connections with other mid- and forebrain regions not generally implicated in the regulation of breathing. The

specific functions for many of these preBotC inputs remain unclear. Although afferent pathways indiscriminately target excitatory and inhibitory neurons in the preBotC, we hypothesized that inputs to the preBotC would map to distinct brain regions based on the inhibitory or excitatory phenotype of the projecting neurons. To test this, mice that express tdTomato only when both Cre and FlpO recombinases are present (Ai65) were bred with mice that express Cre in either inhibitory (*Vgat*^{Cre}) or excitatory (*Vglut2*^{Cre}) neurons. Adult offspring (*Vgat*^{Cre} *or Vglut2*^{Cre}; Ai65) received a unilateral preBotC injection of a retrograde AAV that expresses FlpO recombinase (AAVrg-FlpO), thereby specifically activating tdTomato expression in either inhibitory or excitatory neurons that project directly to the preBotC. This combination of transgenic and viral techniques can identify subpopulations of projecting neurons with high efficiency because only a small amount of a single virus needs to reach the cell body to induce strong reporter labeling. Whole-brain imaging revealed distinct populations of labeled neurons with little overlap between inhibitory and excitatory projections. As expected, there were many projections within the ipsilateral preBotC and projecting neurons clustered in the contralateral preBotC. The tracing confirmed known connections through the ventral respiratory group (VRG) and identified projections from mid- and forebrain regions. Vgat+ projections were found primarily in the rostral ventromedial medulla, zona incerta, amygdala, and the bed nucleus of the stria terminalis. On the other hand, the major areas with Vglut2+ projections were the locus coeruleus, parabrachial nucleus, sensory cortex, hypothalamus, and motor cortex. In all areas there was a bias towards ipsilateral projections. Defining these cell-type-specific inputs to the preBotC will provide an essential foundation for future functional studies to determine how and under what circumstances these circuits influence breathing.

Disclosures: E. Reilly: None. **J. Arthurs:** None. **G. Loginov:** None. **N.A. Baertsch:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: NHLBI R00HL145004 (Baertsch)
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Title: The role of enkephalinergic neurons in respiratory control

Authors: *G. LOGINOV[1], J. ARTHURS[1], E. REILLY[1], W. ATKINSON[2], N. BAERTSCH[1,3,4]; [1]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA; [2]Vanderbilt Univ., Nashville, TN; [3]Pediatrics, [4]Physiol. and Biophysics, Univ. of Washington, Seattle, WA

Abstract: Breathing is a highly dynamic and integrated behavior undergoing continuous changes in response to the metabolic demands and behavioral states of an organism. Opioid pathways have emerged to be of high clinical importance as mu-opioid receptors (MORs) mediate

dramatic decline in breathing frequency and regularity following opioid administration. Nonetheless, little is known about the role of endogenous opioid signaling in respiratory control. This study investigates the role of enkephalins, endogenous MORs ligands encoded by the *Penk* gene, in the ventral respiratory column (VRC) of the medulla. To test whether enkephalinergic neurons of the preBötzinger Complex (preBötC) - the inspiratory rhythm-generating region of the VRC - are necessary for breathing rhythmogenesis, we permanently silenced the region's *Penk+* population via AAV-driven expression of tetanus toxin light chain (TetTox). Using whole-body plethysmography, we recorded the respiratory performance of awake and behaving mice during the 14 days following viral injection. During the second week of testing, we observed unexpected mortality in some experimental but not control animals; post hoc analysis of breathing traces revealed the development of severe tachypnea (rapid and shallow breathing) in succumbed mice. Further, we used RNAscope *in situ* hybridization platform to assay enkephalin co-expression with fast excitatory or inhibitory transmitters marked by *VGluT2* or *VGAT* probes respectively. While preBötC *Penk+* cells expressed *VGluT2 or VGAT,* we detected a higher overlap of enkephalin expression with inhibitory transmitters. Thus, biased silencing of the inhibitory drive in the preBötC network may explain the development of tachypnea in TetTox mice. Still, these observations did not assess the specific contribution of enkephalin, as opposed to other types of signaling, to breathing modulation. To directly dissect enkephalinergic effects on respiratory rhythm, we combined optogenetic and pharmacological approaches in urethane-anesthetized spontaneously breathing adult mice. Brief optogenetic activation of *Penk+* neurons in the preBötC evoked breaths while prolonged stimulation increased the rhythm frequency. Importantly, the opioid receptor antagonist Naloxone caused a small but significant reduction in frequency changes during the light stimulation suggesting that while opioid signaling contributes to the rhythm modulation, the main excitatory drive is likely glutamatergic. Translating these findings into awake and behaving mouse model will allow us to further understand the role of enkephalin in state-dependent control of breathing.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

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Title: Characterizing the concentration-dependent effects of isoflurane on population dynamics of ventral respiratory column neurons

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Abstract: The rhythm underlying breathing is generated by neurons in the ventral respiratory column (VRC). Under urethane anesthesia, the coordinated, rhythmic activity of VRC neurons in mice have been shown to evolve along rotational trajectories through a low-dimensional neural manifold (Nat Neuro 27: 259, 2024). Isoflurane (ISO) anesthesia depresses breathing and presents an opportunity to study respiratory rhythmogenesis at a much lower frequency than normal physiological rates. The latent population dynamics of VRC neurons in mice under ISO anesthesia have not yet been described, nor has the extent to which these rotational dynamics are conserved across different anesthetically modulated states of arousal. This study is testing the hypothesis that ISO alters respiratory network population dynamics in a concentration-dependent manner. All experimental procedures were reviewed and approved by the Seattle Children's Research Institute (SCRI) Institutional Animal Care and Use Committee (IACUC) and followed the NIH and ARRIVE guidelines. Female and male (n = 8, mean age: 15wks) Vgatcre:Ai32 mice were anesthetized with ISO delivered in 100% oxygen and a Neuropixel high-density probe was inserted into the left VRC along the rostral-caudal axis. A 200µm fiberoptic was lowered above contralateral VRC. Temperature was held constant via heating pad. Diaphragmatic activity, heart rate, and single unit activity from the left VRC were recorded during ISO concentrations of 1.5%, 2.0%, and 2.5%. Absence of a paw-withdrawal response was confirmed multiple times during each concentration. To probe the network dynamics, inhibitory optogenetic stimulations were triggered during inspiration or expiration for each ISO concentration. Overall, higher concentrations of ISO caused a more pronounced respiratory depression by eliciting slower respiratory phase transitions without altering the percent time spent in each phase. By applying dimensionality reduction techniques, we characterized the expected rotational latent population dynamics. Importantly, rotational population dynamics changed as a function of ISO concentration such that higher concentrations slowed the rotation speed without altering its trajectory. For all concentrations of ISO, unilateral inhibitory optogenetic stimulations of contralateral VRC increased the respiratory rate when stimulations occurred during inspiration. Conversely, stimulations decreased the respiratory rate when they occurred during the expiratory phase. Future studies are increasing sample size and continuing to characterize how ISO alters the latent neural population dynamics of the VRC.

Disclosures: Z.T. Glovak: None. **N.E. Bush:** None. **J.M. Ramirez:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: NIDA Grant DA009158 (AGH)
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NIDA T32 Grant DA024628 (JW)

Title: The Respiratory Effects of Xylazine-fentanyl Combination in Awake Mice

Authors: *J. WATKINS[1], R. HAHN[1], M. DEMPSEY[1], A. G. HOHMANN[2];
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Abstract: Xylazine is an increasingly widespread adulterant in the illicit opioid supply. The sedative effects of xylazine, an α-2 adrenergic receptor agonist and common veterinary sedative, are viewed as potentiating the intensity and duration of opioid reward. Consequently, xylazine-opioid coadministration has become increasingly common. Despite suggestions that combining xylazine with μ-opioid agonists may increase the risk of fatal overdose in humans, existing preclinical work does not establish whether the coadministration of xylazine with opioids increases the risk or severity of opioid-induced respiratory depression, the primary cause of death associated with opioid overdose.
Here we use whole body plethysmography in awake and unrestrained C57BLJ6 mice of both sexes to evaluate the respiratory effects of xylazine in the presence and absence of the potent synthetic μ-opioid agonist fentanyl. We additionally evaluate the efficacy of naloxone, a μ-opioid antagonist used clinically to reverse opioid-induced respiratory depression, in reversing xylazine-fentanyl coadministration.
Xylazine, when administered alone, produced rapid, persistent, and severe respiratory depression at sub-anesthetic doses after intraperitoneal injection. Xylazine decreased minute ventilation, respiratory frequency, tidal volume, and peak inspiratory flow, while increasing end expiratory pause in comparison to vehicle controls. These effects were prevented by coadministration of the α-2 adrenergic receptor antagonist atipamezole. Animals exposed to combinations of xylazine and fentanyl exhibited more severe respiratory depression than those exposed to the same dose of fentanyl, but only when the mixture included a dose of xylazine that exhibited intrinsic effects. Furthermore, the respiratory effects of xylazine-fentanyl coadministration were only partially attenuated by subsequent injections of naloxone; respiratory parameters reflected the intrinsic effects of the administered xylazine dose rather than restoring breathing to baseline levels. Together, these results suggest that xylazine administration suppresses breathing through interactions with α-2 adrenergic receptors, and that exposure to xylazine may both exacerbate opioid-induced respiratory depression and prevent its full reversal by naloxone. These effects may contribute to lethal respiratory effects after xylazine-opioid coadministration.

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Poster

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Topic: E.08. Respiratory Regulation

Support: NIH R01 HL128970
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AHA 24CDA1270910

Title: Melanocortin receptor 4 agonist, setmelanotide, treats opioid-induced respiratory depression

Authors: *N. WILLIAMS[1], M. R. AMORIM[2], V. POLOTSKY[3], O. AUNG[4], D. S. MENDELOWITZ[3], J. ESCOBAR[5], O. DERGACHEVA[1], F. P. SGAMBATI[6];
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Abstract: The primary cause of death associated with opioids is opioid-induced respiratory depression (OIRD) and obesity is a major risk factor that increases mortality. Naloxone is used to reverse OIRD, but this drug is a competitive antagonist of μ-opioid receptor (MOR) and reverses analgesia, which limits its therapeutic use. Alternative non-opioid receptor antagonist-based approaches to OIRD treatment and prevention are needed. Previous studies suggest that melanocortin 4 receptor pathway (MC4R), which is implicated in body weight regulation, may impact control of breathing. An MC4R agonist, setmelanotide (SET), is approved by FDA to treat genetic obesity caused by abnormal melanocortin and leptin signaling. We hypothesized that SET can treat OIRD in mice. C57BL/6J male mice with diet-induced obesity were treated with IP morphine (10 mg/kg) and then 15 min later with either SET (1 mg/kg IP) or vehicle VEH (IP) in a random order. Breathing was recorded by barometric plethysmography, and pain sensitivity was measured by the tail-flick test. In mice with OIRD, SET induced a 3-fold reduction of the apnea index, from 67 ± 7 to 22 ± 4 events per hour ($p < 0.001$), and decreased apnea duration as compared to the VEH treatment. SET increased respiratory rate from 102 ± 4.5 to 130 ± 5.6 breaths per minute ($p < 0.05$). SET did not affect opioid analgesia. Photostimulation of MC4R+ ChR2-expressing fibers in the parafacial region elicited short-latency postsynaptic current in pre-motoneurons projecting to the phrenic motoneurons in the C3-C4 ventral horns of the spinal cord. In conclusion, SET effectively treated OIRD by increasing respiratory rate and inducing a significant decrease in the number of apneas without decreasing analgesia. Parafacial MC4R (+) neurons are a likely site of respiratory effects of SET.

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Poster

PSTR468: Respiratory Control and Breathing Disorders

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Topic: E.08. Respiratory Regulation

Support: FAPESP 2022/02138-9
FAPESP 2018/15957-2
FAPESP 2020/00201-0

Title: Astrocytes of the lateral parafacial region are sensitive to high CO_2 but play no major role in controlling pulmonary ventilation in mice

Authors: *R. MARTINS SÁ[1], B. H. MACHADO[2], D. J. MORAES[3];
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Abstract: Astrocytes of the lateral parafacial region are sensitive to high CO_2 but play no major role in controlling pulmonary ventilation in miceSá, R. W. M[1]; Machado, B.H.[2]; Moraes, D. J. A[1].[1] Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Brazil.[2]Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.
AbstractStudies indicate that astrocytes in the medullary respiratory chemoreceptive areas are responsive to CO_2, pH, and O_2 levels, and can regulate ventilation. Nonetheless, the influence of astrocytes in the parafacial lateral region (pFL) on central respiratory chemoreception remains uncharted. This study tests the hypothesis that astrocytes of the pFL region, which contain expiratory neurons active during respiratory challenges, control the ventilatory response to hypercapnia of mice. Using Aldh1l1$^{Cre/+}$ERT2 mice aged 15-17 weeks, the experiment involved bilateral injections of AAV-DIO-hM4D(Gi)-mCherry or AAV-DIO-hM3D(Gi)-mCherry into the pFL region. The contribution of pFL astrocytes to ventilatory control was assessed *in vivo* through the activation of DREADDs by intraperitoneal injection of JHU37160 (0.1 mg/Kg) under normocapnic or hypercapnic conditions (7% CO2), using whole-body plethysmography. Additionally, the impact of hypercapnia on intracellular [Ca^{2+}] of pFL astrocytes was measured in medullary slices via multiphoton microscopy using transgenic mice expressing genetically encoded calcium indicator (Aldh$^{cre/+}$/Gcamp$^{flox/+}$). The study received approval from the Institutional Ethical Committee (1079/2022). The findings revealed that JHU37160 did not change ventilation in Aldh$^{cre/+}$hM4D(Gi) and Aldh$^{cre/+}$hM3D(Gq) mice under either normocapnia or hypercapnia. On the other hand, hypercapnia induced a significant increase in intracellular [Ca^{2+}] of pFL astrocytes *in vitro* (p=0.001; 35 astrocytes from 5 separate experiments). These results show that pFL astrocytes are sensitive to hypercapnia in vitro but play no major role in controlling ventilation during hypercapnia in vivo.
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Poster

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Topic: E.08. Respiratory Regulation

Title: The Impact of Neonatal Respiratory Infection on Glia of the Spinal Cord

Authors: *G. L. BLISSETT, K. E. HEDLEY, I. ROWE, J. HORVAT, P. JOBLING, M. A. TADROS;
Univ. of Newcastle, Callaghan, Australia

Abstract: Early life stressors (ELS), including infection, interfere with the activation of glia of the central nervous system (CNS), priming them to act as mediators of neuropathology later in life. While altered activation is well established in the brain, little is known about the impact of ELS on spinal glia. We investigated the impact of neonatal respiratory infection (NRI) upon astrocyte and microglial activation within spinal cord grey matter.Male and female BALB/c mice pups were inoculated intranasally on the day of birth with *Chlamydia muridarum* (CMU; 400 IFU), or sham infected. Mice were left to recover, and tissues collected at adolescence (6wks) and adulthood (12wks) to assess the long-term impacts of NRI. Immunofluorescent antibodies against glial fibrillary acidic protein (GFAP; astrocytes) and ionized calcium binding adaptor molecule 1 (Iba1; microglia) were used to assess morphological indicators of glial activation, in thoracic (T2-T5) and lumbar (L2-L5) spinal levels. Comparisons were made between sensory (dorsal horn: DH) and non-sensory (intermediolateral nucleus: IML, and ventral horn: VH) grey matter regions at these levels, and between sexes. An impact of NRI was noted in both glia at adolescence and adulthood. Significantly, the area covered (%area) by GFAP increased in thoracic VH ($p = 0.01$) and lumbar DH ($p = 0.03$) regions of 6wk CMU male mice. Also, the density of GFAP increased in lumbar DH ($p = 0.0474$) regions of 12wk female CMU mice. Further, %area of Iba1 increased in thoracic IML ($p = 0.02$) regions of 6wk female CMU mice, and lumbar DH ($p = 0.02$) regions in 6wk male CMU mice. Morphological analysis also showed robust regional- and sex-specific alterations in microglia morphology in 6wk CMU mice, including cell number and radius, and the number of branch points and length. While no changes in %area or Iba1 density were noted in 12wk CMU mice, subtle morphological alterations were noted in both thoracic and lumbar DH and VH regions of 12wk male CMU mice. Sex differences in glia of sham mice was also significant in both spinal levels at both ages. This study confirms that NRI, a common ELS experienced in infancy, impacts the activation of spinal astrocytes and microglia in a region- and sex-specific manner. These alterations would significantly impact sensorimotor processing within the spinal cord, for both respiratory and somatic circuitry, and appear to persist long after the initial infection has cleared.

Disclosures: G.L. Blissett: None. **K.E. Hedley:** None. **I. Rowe:** None. **J. Horvat:** None. **P. Jobling:** None. **M.A. Tadros:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.24/J19

Topic: E.08. Respiratory Regulation

Support: Craig H. Neilsen Foundation SCIRTS Grant and Inclusion Supplement #993667
NIH Grant UL1 TR001436

Title: Adeno-associated viral tools to target phrenic afferent neurons

Authors: A. C. MORALES[1], T. C. HOLMES[1], H. HUANG[1], F. SANCHEZ[1], J. J. WILLIAMS[2], *K. A. STREETER[1];
[1]Dept. of Physical Therapy, Marquette Univ., Milwaukee, WI; [2]Dept. of Biomed. Engin., Med. Col. of Wisconsin and Marquette Univ., Milwaukee, WI

Abstract: Previous work from our lab has demonstrated that phrenic afferents play an important role in the recovery of breathing following spinal cord injury. However, tools necessary to trace and enable chemogenetic modulation of phrenic afferent neurons are lacking. While intrapleural injection of several AAV serotypes (i.e., AAV7, AAV8, AAV9) readily transduce phrenic motor neurons, few, if any, phrenic afferents are targeted. Here we validate the transduction of phrenic afferent neurons via intrapleural injection of the capsid variant AAV-PHP.S which has enhanced tropism for peripheral neurons. We hypothesized that delivery of AAV-PHP.S via intrapleural injection would transduce phrenic afferents, but not phrenic motor neurons. To test this hypothesis, we performed bilateral intrapleural injections of AAV-PHP.S (pAAV-PHP.S-CAG-tdTomato; n=6) or saline (n=3) with adult male Sprague Dawley rats. Eight weeks post-injection, we evaluated viral transduction in the C3-C5 dorsal root ganglion (DRG) and spinal cord. All PHP.S treated animals (6/6) showed robust tdTomato labeling in spinal areas associated with sensory control while control rats (3/3) showed no labeling. Specifically, we observed tdTomato labeled cell bodies in C3, C4, and C5 DRGs. Pre-liminary quantification of positive DRG cell bodies showed labeling of ~117 neurons from C3-C5, with the highest expression (~40 neurons) found at C4. We also identified positive labeling within the dorsal roots and dorsal columns. Finally, phrenic afferent projections were identified coursing through the dorsal horn, intermediate grey matter, and area around the central canal. Importantly, we did not detect tdTomato labeling of cell bodies in the ventral horn, suggesting phrenic motor neurons were not labeled. Our findings show that intrapleural injection of AAV-PHP.S can be used to effectively target phrenic afferent neurons. Current work is focused on combining this approach with chemogenetics to manipulate phrenic afferent activity.

Disclosures: A.C. Morales: None. **T.C. Holmes:** None. **H. Huang:** None. **F. Sanchez:** None. **J.J. Williams:** None. **K.A. Streeter:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.25/J21

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: R01HL104101

Title: Igfbp2 and Fxyd1 distinguish subsets of RTN astrocytes and may contribute to disordered breathing in Rett syndrome

Authors: *S. JAHANBANI[1], D. K. MULKEY[2], M. L. OLSEN[3];
[1]Virginia Technol. GBCB PhD Program, Blacksburg, VA; [2]Dept. Physiol. and Neurobio., Univ. of Connecticut Physiol. & Neurobio., Storrs Manfld, CT; [3]Virginia Technol. Neurosci. PhD Program, Blacksburg, VA

Abstract: Igfbp2 and Fxyd1 distinguish subsets of RTN astrocytes and may contribute to disordered breathing in Rett syndromeS.Jahanbani1,3, D.K. Mulkey2 and M.L. Olsen31.Genetics, Bioinformatics, and computational biology, Virginia Tech University, Blacksburg, VA 240612. Department of Physiology and Neurobiology, University of Connecticut, Storrs, CT, USA3. School of Neuroscience, Virginia Tech University, Blacksburg, VA 24061R01HL104101Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder caused by mutations in methyl-CpG-binding protein 2 (Mecp2), a transcriptional regulator highly expressed in the brain. Individuals with RTT demonstrate a constellation of neurological symptoms which begin to present at 12-18 months of age. Among these phenotypes, disordered breathing impacts quality of life and cardiorespiratory arrest is a leading cause of premature death in this disorder. Accumulating evidence from RTT preclinical animal models suggest loss of the CO2/H+ dependent drive to breathe (i.e., respiratory chemoreception) contributes to RTT breathing phenotypes. We and others have demonstrated that neurons, together with astrocytes within the retrotrapezoid nucleus (RTN), contribute to the CO2/H+-dependent drive to breath. Our recently published work using single cell sequencing in the RTN of wild type animals reveals two molecularly distinct astrocyte populations within the RTN based on expression of top 10 global and local distinguishing genes. Unique astrocyte **Cluster 1** expresses high levels of insulin-like growth factor (IGF) binding protein 2 (Igfbp2), which regulates the bioavailability of IGF proteins. Unique astrocyte **Cluster 2** is distinguished by high expression of Fxyd domain containing ion transport regulator 1 (Fxyd1), a membrane protein that regulates Na+/K+ATPase activity. Importantly both Igfbp2 and Fxyd1 are overexpressed in other brain regions in RTT models where they are thought to contribute to cellular dysfunction. Furthermore, Trofinetide – only FDA approved treatment for RTT– limits Igfbp2 and Fxyd1 signaling and has been shown to improve respiratory function in RTT patients. Based on this, we speculate that increased expression of Igfbp2 and Fxyd2 in RTN astrocyte clusters 1-2 disrupt CO2/H+ chemoreception and contribute to breathing problems in RTT.Key WordsRett Syndrome, Astrocytes, Retrotrapezoid Nucleus, Transcriptome

Disclosures: S. Jahanbani: None. **D.K. Mulkey:** None. **M.L. Olsen:** None.

Poster

PSTR468: Respiratory Control and Breathing Disorders

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR468.26/J22

Topic: D.04. Interoception

Support: NIH Grant HL141269
NSF Grant 2334697

Title: Mrgprc11^{+} jugular neurons are critical in the neuroimmune interactions controlling airway constriction

Authors: Y. XING[1], Y. NHO[2], K. LAWSON[3], Y. ZHU[4], W. HANCOCK[3], A. ELLISON[3], M. CHANG[3], ***L. HAN**[3];
[1]Georgia Inst. of Technol., Decatur, GA; [2]Biol. Sci., Georgia Technol., Atlanta, GA; [3]Georgia Inst. of Technol., Atlanta, GA; [4]Hongkong Polytechnic Univ., Hongkong, China

Abstract: The lung is densely innervated by sensory nerves, the majority of which are derived from the vagal sensory neurons. Vagal ganglia consist of two different ganglia, termed nodose and jugular ganglia, with distinct embryonic origins, innervation patterns, and physiological functions in the periphery. Since nodose neurons constitute the majority of the vagal ganglia, our understanding of the function of jugular nerves in the lung is very limited. This study aims to investigate the role of MrgprC11^{+} jugular sensory neurons in a mouse allergic asthma model. Our previous study has shown that MrgprC11^{+} jugular neurons mediate cholinergic bronchoconstriction. In this study, we found that in addition to MrgprC11, several other Mrgpr family members including MrgprA3, MrgprB4, and MrgprD are also specifically expressed in the jugular sensory neurons. MrgprC11^{+} jugular neurons exhibit dense innervation in the respiratory tract including the larynx, trachea, proximal, and distal bronchus. We also found that receptors for IL-4 and oncostatin M, two critical cytokines promoting allergic airway inflammation, are mainly expressed in jugular sensory neurons. Both IL-4 and oncostatin M can sensitize the neuronal responses of MrgprC11^{+} jugular neurons. Moreover, ablation of MrgprC11^{+} neurons significantly inhibited airway hyperresponsiveness in the asthmatic lung, demonstrating the critical role of MrgprC11^{+} neurons in controlling airway constriction. Our results emphasize the critical role of jugular sensory neurons in respiratory diseases.

Disclosures: Y. Xing: None. **Y. Nho:** None. **K. Lawson:** None. **Y. Zhu:** None. **W. Hancock:** None. **A. Ellison:** None. **M. Chang:** None. **L. Han:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.01/J23

Topic: E.09. Motor Neurons and Muscle

Title: Neuroyattam : Study of Physiology & Biomechanics of a Mohiniyattam dancer.

Authors: *S. NAIR[1], J. KANWAL[2], N. SURESH[3], S. TELFER[4];
[1]Stanford Online High Sch., Redmond, WA; [2]Postdoctoral Scholar Res. Associate in Biol. and Biol. Engin., Caltech, Pasadena, CA; [3]Shirley Ryan AbilityLab, Chicago, IL; [4]Dept. of Orthopaedics and Sports Med., Univ. of Washington, Seattle, WA

Abstract: Mohiniyattam is a South Indian classical dance form from Kerala, India that translates to "the dance of Mohini", the celestial enchantress from Hindu mythology. The dance is characterized by graceful movements, soft footwork, hand gestures, and subtle facial expressions. Neuroyattam brings Neuroscience and Mohiniyattam together to study the muscle activation patterns underlying various Adavus (dance sequences). I am a Mohiniyattam dancer and want to understand the underlying physiology and biomechanics of this ancient art form. In this study, we compare muscle activation sequences while dancers perform ten Adavus. We aim to assess whether the timing and pattern of these muscle activations helps classify stylistic differences across dancers, quantification of "gracefulness" in their respective moves, and relative conformance to the reference pattern of a skilled teacher. Gracefulness is in the eye of the beholder however, experienced dancers exhibit smooth transitions in their movements. Seven student practitioners of Mohiniyattam dance participated in this UW IRB approved study (STUDY00019817). Each dancer had eight Delsys Trigno Avanti sensors placed on arm and leg muscles while performing ten Adavus. The sensors recorded real time muscle action potential (EMG) signals, accelerometer coordinates (X,Y,Z), and gyroscope coordinates (X,Y,Z) for angular movements. The integrated EMG, IMU sensors were placed on the left and right sides of the biceps brachii, brachioradialis, rectus femoris, and gastrocnemius lateral head muscles. EMG signals provided quantification of muscle activation timing, sequence and intensity. Relative grace with respect to the teacher's movements was computed for various Adavus by analyzing the accelerometer signals for each dancer. We document the unique muscle activation signatures corresponding to each Adavu and compare the variability and conformance between the student and teacher. Our findings show that most Adavus have stronger activation of the rectus femoris and biceps brachii relative to the gastrocnemius lateral head and brachioradialis, as the Adavus exercise control and movement of muscles closer to the core (Bicep & Thigh) vs. extremities (Forearm & Calf). Understanding the physiology and biomechanics of Mohiniyattam enables the teacher to identify stylistic differences and develop personalized training plans for their students.

Disclosures: S. Nair: None. **J. Kanwal:** None. **N. Suresh:** None. **S. Telfer:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.02/J24

Topic: E.09. Motor Neurons and Muscle

Support: RooWalk-HRW -- FKZ 16SV9069

Title: Decoding Upper Limb Movement: A Recurrent Neural Network Approach for Predicting Muscle Activity Patterns

Authors: M. SCHMIDT[1], ***I. IOSSIFIDIS**[2];
[1]Inst. für Informatik, Ruhr West Univ.of Applied Sci., Mülheim an der Ruhr, Germany; [2]Ruhr West Univ. of Applied Sci., Muelheim an der Ruhr, Germany

Abstract: The upper limbs are critical for performing everyday tasks that require strength, range of motion, and precision. Planning and timing are essential to achieve coordinated movement. Sensory information about the target and current body state is critical, as is the integration of prior experience represented by prelearned inverse dynamics that generate the associated muscle activity. We propose a generative model that uses a recurrent neural network to predict upper limb muscle activity during a variety of simple and complex everyday movements. By identifying movement primitives within the signal, our model enables the decomposition of these movements into a fundamental set, facilitating the reconstruction of muscle activity patterns. Our approach has implications for the fundamental understanding of movement control and the rehabilitation of neuromuscular disorders with myoelectric prosthetics and functional electrical stimulation.

Disclosures: M. Schmidt: None. **I. Iossifidis:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.03/J25

Topic: E.09. Motor Neurons and Muscle

Support: Rehabilitation Engineering Research Center on Sensor Technology Applied to Rehabilitation in Stroke

Title: Force steadiness post stroke varies across different muscles

Authors: ***F. SHI**[1,2], J. SON[3], W. Z. RYMER[2,4];
[1]Northwestern Univ., Chicago, IL; [2]Shirley Ryan Abilitylab, Chicago, IL; [3]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; [4]Northwestern University, Chicago, IL

Abstract: Variations in force output are commonly observed during voluntary sustained isometric contractions. While alterations in force variations in older adults have been widely reported, there is no extensive research on this topic in stroke populations. The adaptations in muscle activation or motor units (MUs) firing behaviors post stroke likely result in impaired motor function, which may manifest as greater force variation. As an essential step towards the

long-term goal of developing a biomarker to monitor motor function for clinical cohorts, this study aims to investigate the changes in force steadiness generated by FDI and elbow flexors in stroke survivors. Five chronic stroke survivors were included in this study. Isometric force was collected from the proximal phalanx of the index finger during finger abduction and from the wrist during elbow flexion. Five force levels were performed on both sides, i.e., 20 - 60% maximum voluntary isometric contraction (MVIC) with 10%MVIC increment, calibrated by the MVIC on the paretic side. Typical force variations from a 5-s segment were shown in Fig 1a & b.Force standard deviation (FSD) was quantified. The relative changes in FSD (FSD_{Norm}) were estimated (FSD_{Norm} = 100*[(FSD(Pare) - FSD(Contra)) / FSD(Contra)]. Linear mixed effects models were implemented to test whether FSD is significantly different between sides and whether FSD_{Norm} shows dependence on force.FSD tends to be greater on the paretic side (Fig 1c & d). During elbow flexion, an increase in FSD on the paretic side is only evident at 60%MVIC, while changes in FSD post stroke are noticeable at low forces during finger abduction. FSD_{Norm} seems to be a function of force during elbow flexion, while there is no clear association of FSD_{Norm} with force during finger abduction (Fig 1e & f).These findings imply that the changes in force steadiness post stroke seem different among muscles. Such discrepancy might be linked to different MU recruitment strategies or distinct changes in MUs firing patterns in FDI and elbow flexors.

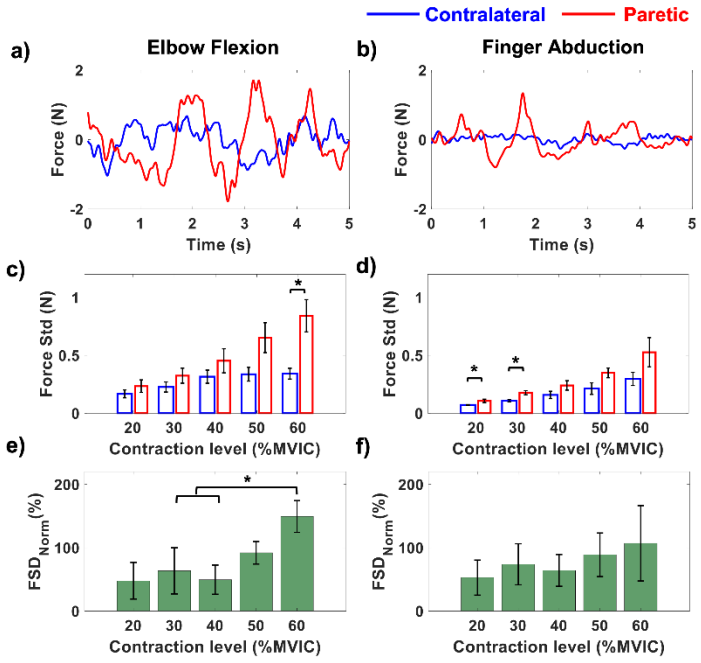

Figure 1.
a) Representative force trials at 50% MVIC for 5s on both sides during elbow flexion
b) Representative force trials at 50% MVIC for 5s on both sides during finger abduction
c) Summary result of force variability across all contraction levels on both sides during elbow flexion
d) Summary result of force variability across all contraction levels on both sides during finger abduction
e) Relative changes in force variability between two sides among all force levels during elbow flexion
f) Relative changes in force variability between two sides among all force levels during finger abduction.

Asterisk indicates a significant difference
*(*p < 0.050)*

Disclosures: F. Shi: None. **J. Son:** None. **W.Z. Rymer:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.04/J26

Topic: E.09. Motor Neurons and Muscle

Title: The effect of background activation on reflex excitability in chronic stroke survivors

Authors: *N. L. SURESH[1], W. Z. RYMER[2];
[1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Shirley Ryan AbilityLab, Chicago, IL

Abstract: Spasticity is a common motor impairment following a hemispheric stroke and is often characterized by hyperreflexia. While the origins of spasticity remain largely unknown, increases in motoneuron(MN) excitability remains a strong possibility perhaps driven by sustained depolarization of the MN pool. Our hypothesis is that the stark differences in muscle reflex output on the spastic side of stroke survivors as compared to the contralateral side, would be reduced or non existent with background muscle activation during reflex testing. To address this we tested the stretch reflex in the biceps brachii on both the affected and contralateral sides of four hemiparetic stroke individuals, using brisk tendon taps during a passive state and with background muscle activity. Bipolar surface EMGs were recorded from both the biceps and triceps brachii muscles. Tendon reflexes were elicited using a tendon hammer, which contained a load cell attached at the point of contact with the forearm. The magnitudes of the surface EMG responses were measured by calculating the root mean square(RMS) of the reflex response. A least squares regression line was fit to the RMS EMG of the reflex response versus the (force)magnitude of the tendon tap(TT) response. The slope of this regression line was compared for the involved and contralateral sides of each subject for both conditions. Three of the four subjects exhibited a substantially greater slope on the impaired side as compared to the unimpaired side under resting conditions. In these subjects, biceps activation did not significantly alter the slope derived from the spastic side yet there was a significant increase in the regression line slope in the contralateral biceps with activation. This data would suggest that the motoneuron(MN) pool on the spastic side is in a hyperexcitable state during rest, thus slight background activation does not result in greater activation of the MN pool, as is observed on the non-spastic side.

Disclosures: N.L. Suresh: None. **W.Z. Rymer:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.05/J27

Topic: E.09. Motor Neurons and Muscle

Title: Ultrasound Stimulation of the Spinal Cord Modulates Corticospinal Excitability

Authors: *S. ABBASIKAMAZANI, L. HOU, H. SOROUSHI, S. BAO, Y. LEI;
Dept. of Kinesiology & Sport Mgmt., Texas A&M Univ., College Station, TX

Abstract: Ultrasound can noninvasively modulate human brain activity, yet it remains unclear whether it can also affect spinal activity. In this study, we investigated the impact of low-intensity ultrasound on the spinal cord by measuring corticospinal excitability and analyzing how different sonication parameters affect the results. A 500 kHz ultrasound transducer, with a focal depth exceeding 140 mm, was utilized to target the C8 spinal cord. Transcranial magnetic stimulation (TMS) was used to measure the corticospinal excitability of the first dorsal interosseous (FDI) muscle, which is innervated by the C8 nerve. The ultrasound stimulus consisted of individual pulses with a pulse repetition frequency of 500 Hz and a duty cycle of 30%, lasting for 500 ms. The ultrasound stimulus was initiated 400 ms prior to administering TMS over the motor cortex hotspot of the FDI muscle. Additionally, the impact of varying the duty cycle and pulse repetition frequency was investigated. Our results showed that ultrasound stimulation decreased the amplitudes of TMS-induced motor-evoked potentials (MEPs) in the FDI muscle, indicating that ultrasound applied to the spinal cord may inhibit corticospinal drive to the muscle. These findings suggest that ultrasound stimulation could be employed to modulate spinal activity.

Disclosures: S. Abbasikamazani: None. **L. Hou:** None. **H. Soroushi:** None. **S. Bao:** None. **Y. Lei:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.06/J28

Topic: E.09. Motor Neurons and Muscle

Title: Visual and Motor Cortex Excitability Are Correlated: A Systematic Review and Meta-analysis of Transcranial Magnetic Stimulation Evidence

Authors: *T. N. M. PHAM[1], S. M. SCHABRUN[2];
[1]Univ. of Western Ontario, London, ON, Canada; [2]The Univ. of Western Sydney, Penrith.

Abstract: Transcranial magnetic stimulation (TMS) research and clinical practice often deliver an intensity determined by the resting motor threshold (rMT) measured at the motor cortex. Another method to establish cortical excitability involves phosphene threshold (PT) measured at the visual cortex. While common approaches, both assume that a singular value of cortical excitability in one cortex can act as a global measurement for other TMS target areas. To evaluate this assumption, we conducted a systematic review and meta-analysis of studies examining both rMT and PT in healthy participants. The results showed a correlation between rMT and PT ($\rho = .40$, 95% CI = [.33, .47], $p < .0001$) based on 16 effect sizes from eight studies, suggesting that values from the motor or visual cortex could serve as a global cortical excitability measure. Three exploratory meta-analyses revealed that PT intensities were higher than rMT, as well as the correlations being stronger when paired pulses were delivered and where rMTs were estimated based on motor evoked potentials (MEPs) > 100 μV. All analyses presented robust

evidence for a PT-rMT correlation, indicating that one TMS measure may be generalized as a global cortical excitability. Further research is needed for a more comprehensive understanding of cortical excitability measured by different TMS methodology.

Disclosures: T.N.M. Pham: None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.07/J29

Topic: E.09. Motor Neurons and Muscle

Title: Paired pulse TMS measures of intracortical inhibition and facilitation are influenced by participant factors and experimental procedures

Authors: *S. HASANI[1], S. COTE[1], T. MOHAMAD[1], D. T. CORP[2], J.-F. LEPAGE[3]; [1]Univ. of Sherbrooke, Sherbrooke, QC, Canada; [2]Deakin Univ., Burwood, Australia; [3]Dept. of Pediatrics, Sherbrooke Univ., Clin. Res. Center, Sherbrooke Univ. Ho, Sherbrooke, QC, Canada

Abstract: Small sample size is an important issue in transcranial magnetic stimulation (TMS) research, often resulting in inconsistent findings. The 'Big TMS Data Collaboration' consists of pooled data from 35 TMS studies, resulting in a comprehensive dataset that allows researchers to better understand how experimental procedures and parameters can influence TMS outcomes. Utilizing this dataset, we conducted a large-scale analysis to explore the influence of baseline motor evoked potential (MEP) amplitude (six groups starting at < 0.4mv, increasing by 0.4 up to > 2mV) and test stimulus (TS) definition (120% of rMT vs 1 mV method) and resting motor threshold (rMT, (%max stimulator output)) on short intracortical inhibition (SICI) and intracortical facilitation (ICF) ratios. The final sample consisted of 273 healthy participants (mean age ± SD = 37.7 ± 18.5 years; 47.3% female) from 14 studies. Our results indicated that higher baseline MEP amplitudes were associated with increased SICI ($f=3.53$, $p=0.004$), and reduced ICF ($f=31.42$, $p < 0.001$). Notably, the strongest differences in SICI were observed between the highest baseline MEP amplitude group (baseline greater than 2.0mV) and the lower amplitude groups (≤ 0.4mV, $p=0.005$; 0.4mV-0.8mV, $p=0.023$). For ICF, individuals with higher baseline MEP amplitudes presented higher ICF ratios. Higher rMT was linked with stronger ICF ($f=4.4$, $p=0.008$), but was not associated with SICI ratios. Lastly, using 120% rMT for TS measurement resulted in stronger ICF compared to the 1 mV method ($t=4.81$, $p < 0.001$). Taken together, our results show that baseline MEP amplitude, rMT, and TS intensity establishment methods may affect the responses of participants to paired-pulse TMS measures. This highlights the importance of implementing a standardized method when performing paired-pulse TMS experiments.

Disclosures: S. Hasani: None. **S. Cote:** None. **T. Mohamad:** None. **D.T. Corp:** None. **J. Lepage:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.08/J30

Topic: E.09. Motor Neurons and Muscle

Support: NIH F31 HD112-86-01A1
Minnesota's Discovery, Research, and Innovation Economy initiative
Neuromodulation Fellowship

Title: Corticocortical control of trunk muscles in young healthy adults:a transcranial magnetic stimulation study

Authors: *E. LECY[1,2], C. MAUPIN[3], J. CHUNG[1], C. D. MACKINNON[4];
[2]Dept. of Neurosci., [3]Div. of Physical Therapy and Rehabil. Sci., [4]Neurol., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: Currently, little is known about the cortical and subcortical control of axial muscles. This study used paired-pulse transcranial magnetic stimulation (TMS), applied over the left trunk region of primary motor cortex, to examine intracortical pathways contributing to the control of the erector spinae (ES at three levels: ES_{T7}, ES_{T12} and ES_{L4}) muscles in 15 young neurotypical adults (age = 22±3 years, 10 females).

Motor evoked potentials (MEPs) were measured with surface EMG sensors placed bilaterally at ES_{T7}, ES_{T12}, and ES_{L4}. Active motor threshold (AMT) was determined via the lowest TMS intensity producing a MEP in ES_{T12} during isometric trunk extension in sitting. Three TMS conditions were tested: single pulse (130% AMT), and two paired-pulse conditions (conditioning stimulus 80% AMT, test stimulus 130% AMT) with inter-stimulus intervals (ISIs) designed to assess short-latency intracortical inhibition (SICI; ISI 3ms) and intracortical facilitation (ICF; ISI 10 ms). TMS was delivered in 15 trials/condition. MEPs were divided into 5 ms time intervals from MEP onset ("time bin") and quantified by measuring the area under the rectified curve (AUC) within each time bin.

Contralateral MEPs were characterized by an initial short-latency, lower magnitude component, followed by a later (8-10 ms) large amplitude component. Across all contralateral muscles, TMS with an ISI of 10 ms (ICF) significantly facilitated the initial component of the MEP over the 0-5 ms time bin by 18.6-27.6% ($p \leq 0.027$), whereas an ISI of 3 ms (SICI) significantly suppressed the later component of the MEP over the 10-30 ms time bins by 23.2-33.4% ($p \leq 0.027$). Across all ipsilateral muscles, TMS with an ISI of 3 ms significantly suppressed the MEP for the 20-30 ms time bins ($p \leq 0.011$), whereas an ISI of 10 ms did not significantly change the MEP (all $p > 0.05$). These differences were consistent across all erector spinae muscles.

These data demonstrate that the effects of paired-pulse TMS on measures of SICI and ICF differ between the initial short-latency and later components of the MEP. The initial component, which is mediated by fast-conducting corticospinal pathways, was significantly facilitated using the ICF protocol (ISI = 10 ms), but not significantly suppressed with the SICI protocol (ISI = 3 ms). In

contrast, the later component of the MEP showed significant SICI, but not ICF. The timing of the later component of the MEP was consistent with a polysynaptic, putative corticoreticulospinal, pathway. Taken together, these results suggest that the intracortical circuits mediating SICI and ICF are different between the corticospinal and putative cortico-brainstem pathways projecting to trunk muscles.

Disclosures: E. Lecy: None. **C. Maupin:** None. **J. Chung:** None. **C.D. MacKinnon:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.09/J31

Topic: E.09. Motor Neurons and Muscle

Support: Minnesota's Discovery, Research, and Innovation Economy Initiative Neuromodulation Fellowship
NIH F31 HD112-86-01A1

Title: Characteristics of transcranial magnetic stimulation responses in the trunk muscles of young healthy adults: evidence for two separate descending systems

Authors: *C. MAUPIN[1], E. E. LECY[2], J. CHUNG[3], C. D. MACKINNON[4];
[2]Neurosci., [1]Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota, Minneapolis, MN, ;
[4]Neurol., Univ. of Minnesota, Minneapolis, MN

Abstract: Two cortical descending systems are thought to play an important role in the control of trunk muscle activity: corticospinal and corticoreticulospinal pathways. The relative contributions of these systems to the control of posture and axial movements are poorly understood. This study characterized the responses to transcranial magnetic stimulation (TMS) over the contralateral motor cortex in four muscles, the erector spinae (ES) at three levels (ES_{T7}, ES_{T12} and ES_{L4}) and external oblique (EO), in 16 young neurotypical adults (age = 22+/-3 years, 10 females). TMS was applied over the trunk region of the left primary motor cortex during sitting. Muscle activation was measured with surface EMG sensors placed bilaterally at ES_{T7}, ES_{T12}, ES_{L4}, and EO. Active motor threshold (AMT) was determined via the lowest TMS intensity producing a motor evoked potential (MEP) in ES_{T12} during isometric trunk extension. TMS was applied from 80-150% of ES_{T12} AMT in 8 randomized blocks of 15 trials. The area under the rectified MEP curve (AUC) was calculated over 5 ms intervals (“time bin”) from MEP onset to characterize the response magnitude. Contralateral MEPs were characterized by an initial short-latency, lower magnitude component, followed by a later (8-10 ms) large amplitude component. Contralateral MEPs had onset latencies ranging from ES_{T7} = 11.5 ms [10.0,13.0] to EO=15.5 ms [13.0,16.5] (reported as median [interquartile range]). Ipsilateral MEPs had onset latencies that were delayed (from ES_{T7} = 12.0 ms [10.5,13.5] to EO = 15.5 ms [13.5,16.5]). At intensities from 110-150% ES_{T12} AMT, the AUC from the 10-20 ms after MEP onset time bins

was significantly larger than the 0-5 ms and 25-30 ms time bins (p<0.001). The 10-20 ms component of the MEP was between 34.5-51.1% larger than the initial component (0-5 ms). The differences between AUC for the time bins were consistent across all contralateral muscles on a rostral-to-caudal gradient. No significant differences in MEP magnitudes (AUC) across any time bins were found for ipsilateral muscles (all p>0.05). These data demonstrate that contralateral trunk muscle MEPs are composed of distinct early and late components, likely reflecting weak input from fast-conducting corticospinal pathways and stronger input from polysynaptic, putative corticoreticulospinal, pathways. These components respond differently across varying TMS intensities. These findings can help us better understand the contributions of changes in corticofugal projections to the control of axial muscles in people with postural disorders associated with aging and neurological disorders, and to design more effective treatment options for postural instability.

Disclosures: C. Maupin: None. **E.E. Lecy:** None. **J. Chung:** None. **C.D. MacKinnon:** None.

Poster

PSTR469: Human Kinematics and Transcranial Motor Stimulation

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR469.10/J32

Topic: E.09. Motor Neurons and Muscle

Title: Effectiveness of Hebbian Stimulation in Hand and Arm Muscles in Humans

Authors: *M. LEE[1], M. A. PEREZ[2];
[1]Shirley Ryan AbilityLab, Chicago, IL; [2]Ctr. for Neural plasticity, Arms & Hands, Shirley Ryan Abilitylab, Chicago, IL

Abstract: Effectiveness of Hebbian Stimulation in Hand and Arm Muscles in Humans
Min-Kyu Lee[1,2], Monica A Perez[1,2,3] [1] Shirley Ryan AbilityLab, Chicago, IL, USA, [2] Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, IL, USA, [3] Edward Hines Jr., VA Medical Center, Chicago, IL, USA
Hebbian stimulation, based on principles of spike-timing dependent plasticity, has been successfully used to enhance corticospinal excitability and functional recovery in humans with spinal cord injury. To further improve the therapeutic effect of this protocol, in the present study, we aim to understand the effect of Hebbian stimulation in proximal and distal arm muscles, which motoneurons receive different corticospinal contributions. We aimed to compare the facilitatory effects of Hebbian stimulation on corticospinal-motoneuronal connections of the biceps brachii (BB) and first dorsal interosseous (FDI) muscles in control subjects. During Hebbian stimulation, corticospinal volleys evoked by transcranial magnetic stimulation (TMS) were timed precisely to arrive at corticospinal-motoneuronal synapses of the BB and FDI muscles 1-2 ms prior to the arrival of antidromic potentials elicited through electrical stimulation of the musculocutaneous and ulnar nerves. Each muscle was targeted during separate sessions using 180 paired pulses on different days. Motor evoked potentials (MEPs) elicited by TMS

were used to assess corticospinal excitability in the BB and FDI before, immediately after, and 30 min after the stimulation. TMS was delivered at 100% of the maximum stimulator output (MSO), above the resting motor threshold for both muscles (FDI=59±11% of the MSO; biceps=67±12% of the MSO). We found that MEP size increased largely in the FDI (by 98±78%) compared with the biceps (by 41±89%) after the stimulation. Thus, our results suggest that corticospinal-motoneuronal facilitation is more prominent in distal hand muscles compared to proximal arm muscles, which might be related to the organization of corticospinal projections. This information will inform the use of Hebbian stimulation, considering muscle-specific adaptations to enhance neurorehabilitation.

Disclosures: M. Lee: None. **M.A. Perez:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.01/J33

Topic: F.01. Neuroethology

Support: Simons Collaboration on the Global Brain

Title: Human-like Vocal Representation in a Parrot Forebrain Motor Area

Authors: *Z. YANG[1], M. A. LONG[2];
[1]New York Univ. Langone Med. Ctr., New York, NY; [2]Neurosci. Inst., NYU Sch. of Med., New York, NY

Abstract: Human speech is a highly flexible sensorimotor act. In contrast, commonly used models for vocal imitation and production - such as the zebra finch - have more limited vocal capacities. In this investigation, we therefore consider the budgerigar, a member of the parrot family that is capable of producing highly flexible vocalizations that adeptly explore a richer acoustic space, including mimicked speech sounds. The forebrain of the budgerigar features a unique neural structure, the central nucleus of the anterior arcopallium (AAC), that strongly projects to vocal motoneurons and likely is involved in song production. To test this hypothesis, we performed silicon probe recordings in AAC and found that neurons within that structure exhibit strong vocalization-related bursting activity, reinforcing the idea that it is playing a role in motor production. Unlike similar forebrain neurons in the zebra finch whose activity is not tied to song acoustics, budgerigar AAC neurons appear to reflect the spectral properties of ongoing vocalizations. We further found that three distinct acoustic elements in the budgerigar repertoire (i.e., quiet low frequency tones, vowel-like harmonic elements, and consonant-like broadband sounds) map onto different regions in the populational neural space. Additionally, within the harmonic representation, the AAC population linearly maps vocal pitch onto a single axis, facilitated by single AAC neurons encoding pitch systematically. Across budgerigars, the geometry of the AAC representation is strikingly consistent, supporting the notion of a universal

articulatory map. Given the orderly representation of vocal elements, including pitch, the budgerigar AAC is the first human-like forebrain representation of vocalization described in an animal model.

Disclosures: Z. Yang: None. **M.A. Long:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.02/J34

Topic: F.01. Neuroethology

Support: NIH R01 NS075044
Simons Global Brain

Title: Dissection of local synaptic connectivity in vivo with simultaneous whole-cell patch clamp and silicon probe recordings

Authors: *M. B. PHILLIPS[1], J. KIM[2], M. A. LONG[2];
[1]NYU Neurosci. Inst., New York, NY; [2]Neurosci. Inst., NYU Sch. of Med., New York, NY

Abstract: Complex motor sequences often rely on the coordinated activity of excitatory projection neurons and local circuit inhibitory neurons, but bridging the gap between the cellular and network mechanisms underlying sequence generation has proven difficult. The zebra finch courtship song is a complex, yet highly tractable, motor sequence patterned by a key forebrain region, HVC. During song, excitatory projection neurons in HVC generate a precise, sparse sequence of activity, with each neuron contributing a burst at an invariant timepoint in the sequence throughout the song. Models of sequence generation within HVC have focused on local excitatory connections, and the role of inhibition in this process remains uncertain. Furthermore, we have recently found that molecularly defined interneuron subtypes in HVC exhibit distinct activity profiles, but whether these inhibitory subtypes differentially contribute to song-related network dynamics is unknown. To dissect local connectivity in HVC, we developed a hybrid electrophysiological technique that we term MERgE (**M**ulti**E**lectrode **R**ecording and conductance (**g**) **E**lectrophysiology). MERgE consists of *in vivo* whole-cell patch clamp recordings of single HVC neurons alongside simultaneous silicon probe recordings of HVC population spiking activity. This recording configuration allows us to directly measure the precise synaptic strength of dozens of simultaneously recorded neurons onto a single postsynaptic cell. We use voltage-clamp recordings to isolate and observe short-latency inhibitory or excitatory postsynaptic events that reliably follow spikes from identified neurons recorded via silicon probe, enabling a view at both behaviorally-relevant network activity as well as detailed synaptic information (e.g., amplitude and dynamic properties of unitary postsynaptic events for neurons measured on the silicon probe). With this hybrid approach, we can begin to

dissect the influence of local processing underlying the performance of a premotor network sequence.

Disclosures: M.B. Phillips: None. **J. Kim:** None. **M.A. Long:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.03/J35

Topic: F.01. Neuroethology

Support: NIH R01 NS075044
Simons Global Brain

Title: Excitatory and inhibitory connectivity underlying precise sequence generation in the zebra finch HVC.

Authors: *J. KIM[1], M. A. LONG[2];
[1]NYU Neurosci. Inst., Brooklyn, NY; [2]Neurosci. Inst., NYU Sch. of Med., New York, NY

Abstract: The sequential activity of neurons has been observed in neural circuits of many species and has been proposed to play a central role in numerous behavioral processes. Despite its ubiquity, we still have relatively little understanding of the cell-type specific wiring that underlies precise sequence generation. We investigate a cortical structure in the zebra finch brain called HVC (proper name), where excitatory (E) premotor neurons fire in a sparse stereotyped sequence during courtship song performance. Local circuit inhibitory interneurons (I) are necessary for normal song behavior, and several conflicting models exist to explain their involvement in sequence generation. To gain traction on this problem, we analyzed the population activity of HVC neurons in behaving zebra finches using high-density silicon probes, relating putative E and I connections with the observed role in song-related network activity. We found that HVC is dense with strong local E and I connections. Furthermore, we measured an overrepresentation of various network motifs, including the reciprocal (E ↔ I) and feedforward inhibitory (E → I → E) motifs, suggesting a role for fast inhibitory feedback in the generation of a sparse excitatory sequence. In addition, we found a small subset of “hub” interneurons, characterized by abnormally many incoming excitatory and outgoing inhibitory connections. Auto correlograms of hub interneurons were qualitatively similar amongst each other, suggesting that these neurons could represent a specific interneuron subtype. Next, spiking activity of individual HVC interneurons during singing is characterized by a temporally precise sequence of bursts. Using putative E → I connections, structured bursts of HVC interneurons are explained by bursts of putative presynaptic excitatory neurons in HVC. These results are a step towards understanding the specific higher order connectivity patterns that enable sequence generation in a behaviorally-relevant forebrain circuit.

Disclosures: J. Kim: None. **M.A. Long:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.04/J36

Topic: F.01. Neuroethology

Title: Behavioral and hormonal regulation for acceleration of vocal development

Authors: *H. ZHANG[1], N. TOJI[2], K. WADA[3];
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Abstract: Behavioral and hormonal regulation for acceleration of vocal development
Heng Zhang[1], Noriyuki Toji[2], Kazuhiro Wada[1,2]
[1]Graduate School of Life Science, Hokkaido University, Sapporo, Hokkaido, Japan[2]Faculty of Science, Hokkaido University, Sapporo, Hokkaido, Japan
AbstractThe sensitive period of vocal learning is a critical development window for acquiring complex vocal gestures, such as human speech and birdsong. Zebra finch (*Taeniopygia guttata*) learn their songs during the sensitive period by memorizing and mimicking tutor song models. Testosterone, a sexual hormone, and singing practice during the sensitive period are crucial for the development of vocal learning. However, the precise interpretationships between these two factors and the neural mechanisms underlying vocal learning plasticity remain unknown. We first focused on the ontogeny of vocal plasticity under testosterone administration (T+) before the onset of babbling in juvenile zebra finches. T+ juveniles started singing highly variable subsongs, similar to those of normal birds. However, they rapidly produced sequentially and acoustically crystallized songs within a week after initial singing, suggesting the potential effect of testosterone on HVC and the robust nucleus of arcopallium in the vocal motor circuits. Song development in T+ birds was approximately 10 times faster than that in normal song development. In contrast, singing prevention in T+ juveniles during this period effectively prolonged the state of high vocal variability in their songs, highlighting the necessity of vocal practice for decreasing vocal plasticity under high testosterone conditions. In addition, T+ juveniles generated more intense singing practice during the first week compared to normal juveniles, indicating a link between accumulated singing practice and decreased vocal plasticity. These results suggest that the transcriptional impacts are mediated by the regulation through androgen receptor and singing-driven activity-dependent genes, leading to a decrease in vocal plasticity.

Disclosures: H. Zhang: None. **N. Toji:** None. **K. Wada:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.05/J37

Topic: F.01. Neuroethology

Support: OHSU Tartar Fellowship (CRO)
National Geographic Society 51460-18 (CRO)
NSF IOS-1456302 (CVM)
Konishi Neuroethology Research Award (MFV)

Title: Vocal change over a decade in a free-living population of black jacobins

Authors: *C. OLSON[1], C. V. MELLO[2], C. DUCA[3], S. RODRIGUES SILVA[3], A. RICO-GUEVARA[4], M. FARIAS-VIRGENS[5];
[1]Midwestern Univ., Glendale, AZ; [2]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ. Sch. of Med., Portland, OR; [3]Pontifícia Univ. Católica de Minas Gerais, Belo Horizonte, Brazil; [4]Dept. of Biol., Burke Museum of Natural History and Culture, Univ. of Washington, Seattle, WA; [5]Biol., Univ. of Washington, Seattle, WA

Abstract: Black jacobins are hummingbirds from the basal Topaz clade, common in the Atlantic Forest of Brazil. Their vocalizations have a mean fundamental frequency of 11.5 kHz with rapid oscillations that range from ~10-14 kHz, which is remarkable as this range is well above the established limit of typical avian hearing (up to 8-9 kHz). Black jacobins typically emit their vocalizations during inflight displays at short distance to other conspecifics, whereas we have not observed them vocalizing to other species, or other species responding to their vocalizations. Based on recordings from individuals in captivity, these vocalizations are produced by both sexes and older juveniles, and are represented by a single song type per individual. Given the unique biodiverse habitat where they occur, these high-frequency vocalizations open new directions in the behavioral ecology of animal communication. To address possible temporal patterns of variation, we have compared black jacobin vocalizations recorded at the Instituto Nacional da Mata Atlantica over the past decade (2015 - 2024). In 2015-16 the most common pattern was a 3-syllable triplet, each syllable with distinct features that varied across recorded birds. Starting in 2019 we noted the mixed occurrence of 2- and 3-syllable vocalizations, and by 2022 the 3-syllable utterances had been entirely replaced by 2-syllable ones, a pattern that continued in 2024. We also note the occurrence of some seemingly transitional vocalizations in 2019, where the first two syllables appeared to merge, leading to a longer 1st syllable followed by a short 2nd (former 3rd) syllable. This mixed pattern was also noted in 2022 in roughly half the vocalizations sampled, whereas the remainder were of a simpler pattern of two syllables with identical duration and acoustic structure. The black jacobin's ability to produce and perceive these fine temporal patterns points to their remarkable vocal-motor and sensory abilities. These data set the stage for more extensive investigation of the acoustic biology of this species, the potential role of vocal learning in these changes, and presents a valuable conceptual model for future research on avian vocal communication in complex environments.

Disclosures: C. Olson: None. **C.V. Mello:** None. **C. Duca:** None. **S. Rodrigues Silva:** None. **A. Rico-Guevara:** None. **M. Farias-Virgens:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.06/K1

Topic: F.01. Neuroethology

Title: Characterizing auditory responsivity in female zebra finch HVC

Authors: *A. SAVOY[1], D. MARGOLIASH[2];
[1]Univ. of Chicago, Chicago, IL; [2]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: The zebra finch is a champion species of vocal learning and production, with males producing highly precise songs and females evaluating individual differences in male singing. The foundation of male song includes auditory learning early in development and auditory feedback-mediated sensorimotor learning during development that extends into adulthood. Studies in females, who do not sing, have demonstrated their extraordinary auditory perception abilities as adults, as well as their sensitivity to developmental auditory experience and social context. Many studies in males have focused on the sensorimotor integration area HVC, which expresses state-dependent higher-order song-related auditory responses. Despite the much smaller volume of female zebra finch HVC as compared to males, recent evidence shows robust anatomical connectivity between HVC and other “song system” areas in females. We hypothesize that this circuitry is involved in female auditory processing, song evaluation, and call interactions, which has been investigated only in a few studies. Our study aims to characterize the auditory responsivity of HVC in female zebra finches when exposed to male vocalizations. To date we have used high-density extracellular probes for acute and chronic recordings in awake female zebra finch HVC. Birds were exposed to a variety of male vocalizations and social interactions. Response patterns implicate involvement of HVC in the nuanced perceptual discrimination capability that female zebra finches are known to possess, with varying responsivity depending on her familiarity with the stimulus and relationship to the male. These findings potentially offer new insights into the role of HVC in female auditory perception and contribute to our understanding of the neural bases of social communication and mate choice.

Disclosures: A. Savoy: None. **D. Margoliash:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.07/K2

Topic: F.01. Neuroethology

Support: Internal funding
NIDCD: DC008854

Title: Encoding novel sounds drives dynamic changes in lateralization

Authors: *B. FUREST CATALDO[1], L. YANG[2], P. DADIKA[1], D. S. VICARIO[3];
[1]Psychology, Rutgers Univ., Piscataway, NJ; [2]CUNY Sch. of Med., New York, NY;
[3]Psychology, Rutgers The State Univ. of New Jersey, Piscataway, NJ

Abstract: Lateralized brain systems serve learned vocalizations in both humans and songbirds; adult Zebra finches (ZFs) show right-lateralized responses in the auditory forebrain caudomedial nidopallium (NCM). We now explore the ontogeny of this asymmetry and its stability in adults by passively exposing ZFs to novel sounds and assessing lateralized activity with chronic and acute electrophysiology. First, we show that adult ZFs (>120d post-hatch, phd) exhibit a transient reversal to atypical left-lateralization followed by a return to right-biased activity when exposed to a novel heterospecific (canary) auditory environment for extended periods. Birds tested after return show enhanced behavioral discrimination of novel canary song stimuli not seen after reversal alone. This suggests that left-lateralization is induced when new sound statistics are being encoded while the return to right-lateralization reflects consolidated mapping of canary song features. Second, we probed this process by sequentially exposing adult ZFs to two novel acoustic environments (canary and budgerigar). Results showed two complete cycles of dynamic shifts - right-to-left reversal and left-to-right return - one for each environment, suggesting that lateralized plasticity mechanisms are engaged by novel sound statistics. Further, acute recordings in NCM after return showed improved neural decoding of test stimuli from both novel species' repertoires, Finally, the ontogeny of lateralization was tested longitudinally by exposing developing ZFs (40-120 phd) to different rearing environments, prompted by earlier work showing that developmental auditory experience is necessary for lateralization in adulthood. We now find that auditory activity is left-lateralized early in development and later transitions to right-lateralization. Subsequent recordings in adult NCM show lasting effects of rearing environments on auditory processing. Together, we suggest that the dynamic changes seen in these paradigms reflect the learning of new stimulus statistics: encoding of novel sounds in the young bird engages left-biased activity from which adult right-bias emerges. Adult ZFs in novel environments show similar plasticity when novel stimulus statistics engage the process of reversal during learning followed by return to a new steady-state. Thus, our findings challenge the notion that lateralization is determined and fixed in adulthood. We propose that exposure to new information engages the two hemispheres differently than familiar inputs, and access to the newly encoded information is enabled once the brain has returned to its typical pattern of lateralization.

Disclosures: B. Furest Cataldo: None. **L. Yang:** None. **P. Dadika:** None. **D.S. Vicario:** None.

Poster

PSTR470: Vocal/Social Communication: Physiology and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR470.08/K3

Topic: F.01. Neuroethology

Support: Kenneth A Suarez Research Fellowship Midwestern University

Title: Behavioral induction of retinoic acid signaling in the zebra finch vocal circuit

Authors: *S. WATCHALOTONE[1], C. R. OLSON[2];
[1]Col. of Osteo. Med., [2]Dept. of Physiol., Midwestern Univ., Glendale, AZ

Abstract: Vitamin A signaling in the brain is well-established, yet its regulation is not understood. The conversion of retinol to retinoic acid is achieved by tissue-active enzymes, including ALDH1A2, a marker of vocal nuclei in the vocal forebrain circuit. We tested the hypothesis that vocal behavior and social context upregulates ALDH1A2 expression, akin to how EGR1 is induced with female-directed or undirected song. Male zebra finches (300-400 days old; N=18) were behaviorally conditioned to produce (a) female-directed, (b) undirected song, or (c) were non-singing controls (n=6/trmt). Birds were sacrificed at 2 hrs after peak song to allow gene induction, then brains were blocked for cryosectioning and measurement of expression by ISH. Slides were labeled for ALDH1A2 and EGR1 expression and analyzed for cell density and expression indices of soma within vocal nuclei. Relationships of vocal behavior and EGR1 to vitamin A signaling were tested with Generalized Linear Models. EGR1 and cell density in HVC and LMAN was positively related to singing, and expression was highest with female-directed song, intermediate with undirected song, and reduced in controls, relative to surrounding tissue. In contrast, ALDH1A2 expression in HVC was increased by female-directed song, whereas expression with undirected song was similar to the silent controls. A non-significant pattern of low ALDH1A2 expression in LMAN exists in the undirected song group, while the female-directed song and silent controls were similar. A strong relationship between ALDH1A2 and EGR1 cell density in HVC is particularly pronounced with female-directed song. Our findings that behavior reinforces retinoic acid signaling reveal an important distinction in vocal circuit activation related to vitamin A signaling. It depends both on (1) the amount of singing, and (2) the social context. Undirected singing activates the cortical-striatal circuit (HVC-X) for the learning and maintenance of song, while female-directed song relies on a direct circuit (HVC-RA) while suppressing the cortical-striatal loops. Our discovery that female-directed song increased ALDH1A2 parallels studies that implicate HVC in context-dependent singing. Social context thus potentially alters the expression of hundreds of genes that are under its transcriptional control. Alternatively, undirected song may also result in decreased expression in LMAN but not HVC, and mirrors studies that show undirected song to suppress FOXP2 expression in songbird area X, a pathway rich in RARβs. These findings reinforce the role of micronutrients (vitamin A) in mechanisms of memory formation and learned motor patterns.

Disclosures: S. Watchalotone: None. **C.R. Olson:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.01/K4

Topic: F.03. Stress and the Brain

Support: NSF PRFB 2208822

Title: Unraveling the long-term effects of neonatal predator odor exposure on social reward motivation in rats

Authors: *A. CUARENTA, K. MESAPE, D. A. BANGASSER;
Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Adversity experienced early in life can impact reward-related behaviors and increase the risk for the development of psychiatric disorders. Much of the current research has focused on drugs of abuse, but the effect of early life adversity on natural rewards, including food and social rewards, remain understudied. My previous research has shown that rats exposed to a predator odor exposure (POE) show a show a reduction in juvenile social play behavior. I am now extending this work to determine whether these changes in rewarding social behaviors extend beyond adolescence and into adulthood. In our current study, we use the same POE model to assess the impact of early life adversity on the motivational drive for both food and social reward in Sprague Dawley rats. Rat pups are exposed to the predator odors of bobcat, rat, and ferret on postnatal days 1, 2, and 3 for 5 minutes each day, respectively. We then raised our animals to adulthood to assess the impact of POE on the motivation for natural rewards in adulthood. We conducted oral sucrose self-administration and social self-administration using MedPC Operant Chambers to assess how POE may affect the motivation for sucrose and social interactions. Our preliminary behavioral analysis demonstrates that rats exposed to POE during the neonatal period show a reduction in the motivation for social reward relative to controls. This behavioral change is reward specific as animals exposed to POE show no difference from controls in their motivation for sucrose rewards. These results suggest that the effects of POE on motivation for natural rewards are reinforcer- dependent. Altogether we are developing a nuanced understanding of how early life adversity alters the motivation for reward.

Disclosures: A. Cuarenta: None. **K. Mesape:** None. **D.A. Bangasser:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.02/K5

Topic: F.03. Stress and the Brain

Support: KAKENHI 23K18257
KAKENHI 22H03456

Title: Post-weaning social isolation-induced aggression is suppressed by umami ingestion of monosodium aspartic acid in an ADHD model rat

Authors: Y. NISHIMURA[1], D. MUSTIKA[1,2], S. UENO[1], C.-G. JUNG[1], N. TAJIRI[1], *H. HIDA[1,2];
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Abstract: We previously reported that the ingestion of an umami substance, monosodium glutamate (MSG), decreased post-weaning social isolation (PWSI)-induced aggression in a rat model of attention-deficit hyperactivity disorder model (SHR/Izm), proving that the MSG effect was mediated by the vagus nerve activating intermediate part of the nucleus of solitary tract (iNTS) and modulating central amygdala activity. However, it is unknown whether umami substances other than MSG have similar effect on PWSI-induced aggression. In this study, we challenged to know whether monosodium aspartic acid (MSA), an umami substance which chemical structure is similar to MSG, resulted in similar reduction of PWSI-induced aggression like MSG. PWSI was given to escalate aggressive behavior: SHR/Izm was individually housed and 60 mM MSA was orally ingested from postnatal day 25 for five weeks. The resident-intruder test, that is conducted for 10 minutes per day during the subjective night for 3 consecutive days, was performed from P61 for a detailed analysis of aggression, including the frequency, duration, and latency of anogenital sniffing, aggressive grooming, and attack behavior. The open field test was also performed at P60 to investigate anxiety-like behavior. Immunohistochemistry of c-Fos expression was conducted in iNTS and the aggression-related brain areas to investigate the effect of MSA ingestion on aggression. MSA ingestion during the period of development caused no body weight increase but the increase of drinking volume and urine volume. The Open field test revealed no significant effect of MSA on anxiety: no significant differences in the entrance into center part of arena and total walk length were shown between MSA-ingested group and controls. The resident-intruder test revealed that MSA ingestion resulted in reduction of PWSI-induced aggression: both the number and total time of attacks are significantly changed in MSA-ingested group. Significant increase of c-Fos positive cells was shown in iNTS by MSA ingestion. These data indicate that MSA ingestion also reduces PWSI-induced aggression in SHR/Izm, suggesting that MSA probably binds umami receptor on the enteroendocrine cells in the gut.

Disclosures: Y. Nishimura: None. **D. Mustika:** None. **S. Ueno:** None. **C. Jung:** None. **N. Tajiri:** None. **H. Hida:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.03/K6

Topic: F.03. Stress and the Brain

Support: MOMINFLAM-ISS20-88bc10d8839b

Title: Omega6-omega3 fatty acids dietary imbalance during pregnancy increases emotionality and stress response in the offspring in an animal model of maternal obesity

Authors: C. MUSILLO[1], M. SAMÀ[1], A. BERRY[1], ***F. CIRULLI**[2];
[1]Inst. Superiore Di Sanità, Rome, Italy; [2]Inst. Superiore Di Sanita', Rome, Italy

Abstract: Maternal obesity is considered a detrimental condition for the developing fetus, ultimately increasing the risk for neurodevelopmental and psychiatric disorders. However, specific mechanisms underlying this association still need to be elucidated. High-fat diet (HFD) consumption is characterized by an imbalance between Omega-6 and Omega-3 (n-6, n-3) polyunsaturated fatty acids (PUFA), indeed obese women show a high n-6 to n-3 PUFA ratio. We hypothesized that, in the context of maternal obesity, a high n-6 to n-3 PUFA ratio may result in an insufficient Omega-3 supply to the fetal brain, ultimately disrupting neurodevelopment. Thus, we tested whether maternal supplementation with Omega-3, by re-balancing the n-6 to n-3 PUFA ratio, might be a suitable prevention strategy. Female mouse C57BL6 breeders were fed either an HFD with a high n-6 to n-3 PUFA ratio (carbohydrate 26%, protein 16%, fat 58%, n-6 to n-3 ratio=120, energy 5.56 kcal per g) or a control diet (CD, carbohydrate 73%, protein 16%, fat 11%, n-6 to n-3 ratio=7, energy 4.07 kcal per g) before and during pregnancy. After 4 weeks on the diet, half received a dietary Omega-3 supplementation (n-6 to n-3 ratio=1) for 6 weeks, until delivery. Maternal anxiety-like behaviors (Marble burying test) were assessed during gestation. The emotional profile (Novelty suppressed feeding test) and the neuroendocrine response to restraint stress were evaluated in male and female offspring. Data were analyzed using ANOVA with prenatal diet (HFD vs CD) and supplementation (Omega-3 vs Vehicle) as between-subjects factors. Sidak's post hoc comparisons were performed. Our preliminary results show that an HFD with a high n-6 to n-3 PUFA ratio increases maternal anxiety-like behaviors, as indicated by an increased number of marbles buried resulting in greater emotionality in the offspring. In particular, maternal HFD increased behavioral disinhibition in the novelty-suppressed feeding test in the adolescent offspring, as revealed by a reduced latency to reach the food pellet in the center of the arena. Evaluation of the hypothalamic-pituitary-adrenal axis reactivity also revealed increased corticosterone release in response to stress. We are currently assessing brain inflammation and the preventive effect of Omega-3 supplementation. Preliminary data indicate a trend for such dietary intervention in reducing anxiety behaviors in pregnant females. In conclusion, our data indicate negative effects of dietary imbalance between Omega-6 and Omega-3 fatty acids in pregnant females, with long-term disruption of emotional and neuroendocrine regulations in the offspring. Funding: MOMINFLAM-ISS20-88bc10d8839b

Disclosures: C. Musillo: None. **M. Samà:** None. **A. Berry:** None. **F. Cirulli:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.04/K7

Topic: F.03. Stress and the Brain

Support: The Jean Phillips Shibley Endowment (T.J.G.)
Department of Biobehavioral Health, Pennsylvania State University
Minciencias Fulbright Colombia (C.N.),

Title: Adolescent social stress increases anxiety-like behavior in male mice but does not alter health risk-related biomarkers in the frontal cortex

Authors: *C. NOVOA[1], T. J. GOULD[2];
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Abstract: Adolescence is a period of adaptation to environmental demands and represents a window of increased vulnerability to exposures with detrimental effects on mental and physical health later in life. Disruptions of the social environment during this stage profoundly impact individuals' health trajectories. Here, we studied the long-term effects of 2-week social stress on anxiety-like behaviors and health risk-related biomarkers across several organs using 35-day-old male C57BL/6J mice. We assessed these indicators in adulthood during 2 periods: 1 and 3 months after adolescent stress. To evaluate the effects on adult anxiety-like behaviors we used elevated plus maze and open field tests. To determine cumulative health-related risk we analyzed absolute telomere length and mitochondrial DNA copy number (mtDNAcn) in blood, liver, and brain with qPCR assays. We also monitored body weight throughout the study. In the elevated plus maze, stress reduced exploration of the open arms and head dipping across both time windows, suggesting an enduring enhancement of anxiety-related behaviors. In the open field, stress increased locomotion only during the 1-month window, and had no effects on time in the center, suggesting that enduring alterations of anxiety-related behaviors are modulated by environmental features. We also observed that stress impaired body weight gain and stressed mice remained underweight the month following termination of stress, highlighting potential biological consequences of adolescent social stress. Contrary to our expectations, we did not see differences in telomere length or mtDNAcn in the frontal cortex, but there was a significant interaction between stress exposure and time window for the mtDNAcn in the liver. This suggests that adolescent social stress may alter mitochondrial dynamics in a time and system-specific manner and may indicate the involvement of distinct regulatory mechanisms in different organs. In line with this assumption, we observed that mtDNAcn differed across tissues: the frontal cortex showed higher mtDNAcn compared to the blood in both time windows, and comparable levels to the liver only at 1 month, but elevated levels at 3 months. Additionally, mtDNAcn correlated between the liver and blood, but neither of these tissues correlated with the frontal cortex, suggesting that brain mitochondrial dynamics may differ from other body systems. These results show the enduring consequences of adolescent social stress on mental health-related variables and highlight the complexity of biological mechanisms by which early life stress impacts different body systems to produce its pervasive effects on health later in life.

Disclosures: C. Novoa: None. **T.J. Gould:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.05/K8

Topic: F.03. Stress and the Brain

Support: NIDA 5U01DA043098
ONR N00014-19-1-2149
The Hope for Depression Research Foundation (HDRF)
The Pritzker Neuropsychiatric Research Consortium

Title: A History of Early Life Stress Shifts Network Patterns of Neural Activation in Response to Social Defeat in Adulthood: A Fos-TRAP Study

Authors: *P. MARAS[1], K. L. HILDE[2], H. KHALIL[3], D. MURRA[4], S. J. WATSON[5], H. AKIL[1];
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Abstract: Stress is a major risk factor for mood disorders, particularly when it overlaps with critical windows of brain development. Indeed, epidemiological data suggest that stress experienced during early life is often linked to long-term emotional dysregulation, as well as heightened stress vulnerability. Understanding the mechanisms through which developmental stress shapes how the brain processes and responds to stress throughout life remains a major challenge. To this end, the current study examined the effects of early life stress (ELS) on later stress processing using FosTRAP2 transgenic mice, in which the expression of an indelible tdTomato signal is driven by the Fos promotor (activity-dependent) and is also tamoxifen-dependent, thereby allowing for the permanent labeling of activated neurons during an experimenter-controlled time window. To model ELS, a subset of litters was exposed to daily maternal separations (postnatal days 10 - 17), whereas control litters were standard-facility reared. As adults, ELS and control mice were exposed to 10 days of chronic social defeat stress (CSDS) or control rotation (CR). Tamoxifen was injected on the final day of CSDS/CR to capture neural activation, and mice then underwent a sequence of behavioral testing.
Using a high-throughput, brain-wide cell counting approach, we quantified neural activation across a total of 72 brain regions. Although traditional cell-count comparisons failed to identify significant effects of ELS within any given region, when we applied correlational network analyses, we found compelling shifts in network patterns that varied by ELS history. In the absence of ELS, adult CSDS provoked a network of activation in which the medial hypothalamic zone was the top node, correlating with several other hypothalamic and amygdala sub-regions. When mice had a history of ELS, however, CSDS resulted in a network now centered around the bed nucleus of the stria terminalis (BST), with correlations primarily limited to septal nuclei. In addition to these network shifts, we found that activity levels of some regions during the defeat predicted later social interaction scores, but that relationship again depended on ELS history. In standard-reared mice, for example, the activation of BST during CSDS was positively correlated

with social interaction ratios, but in mice that had ELS history, the relationship between BST activity and behavior was lost. Together, these data suggest that early stressful experiences can have long-lasting effects on the functional connectivity of stress-responsive circuits, shifting the regional nodes that drive networks of brain activation and ultimately behavior.

Disclosures: P. Maras: None. **K.L. Hilde:** None. **H. Khalil:** None. **D. Murra:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.06/K9

Topic: F.03. Stress and the Brain

Support: Northeastern PEAK Award

Title: Effects of early life adversity on prosocial behavior: insights into motivation and underlying neural circuitry

Authors: *A. LYNCH, J. M. BRETON, H. C. BRENHOUSE;
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Abstract: Early life adversity (ELA) is the exposure to negative experiences during childhood, including abuse and neglectful parenting behaviors. Experiencing ELA increases the risk for developing mood and conduct disorders, both of which are characterized by changes in social engagement. ELA is also associated with difficulties in emotional regulation, which may affect an individual's ability to empathize. Empathizing with, comforting, and helping another in distress are prosocial interactions that are essential for the establishment of peaceful societies and positive relationships. However, little is known about how ELA impacts empathy related behavior, including prosocial behavior. Prior research has established that rats will demonstrate prosocial behavior by helping to release a trapped conspecific from a restrainer. In order to test how ELA influences prosocial behavior and underlying neural circuitry, the current study utilized a maternal separation paradigm (MS), and tested adult MS or control-reared male and female rats in a helping behavior task (HBT) with a trapped cagemate. Rats were tested over three weeks for consistency of helping behavior and were perfused on the final test day to assess brain expression of the immediate early gene, c-Fos. Interestingly, we found that MS-reared rats showed faster and more consistent helping behavior than control reared animals. In addition, MS-reared rats displayed increased social behavior (such as rough and tumble play) upon release of the trapped rat, indicating that ELA influences social dynamics with a cagemate. Furthermore, preliminary data showed increased c-Fos expression in the nucleus accumbens of MS-reared rats following the HBT. Continued work will assess whether observed changes in behavior are related to c-Fos levels in additional brain regions associated with social decision making.

Together, these studies provide insight into the neurodevelopmental changes that influence prosocial behavior, and help explain how ELA drives changes in social engagement.

Disclosures: A. Lynch: None. **J.M. Breton:** None. **H.C. Brenhouse:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.07/K10

Topic: F.03. Stress and the Brain

Support: South African Medical Research Council (SAMRC)

Title: Why men rape perspectives from incarcerated rapists in a KwaZulu-Natal prison, South Africa

Authors: *L. QULU;
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Abstract: Sexual offending is a global problem but is particularly prevalent on the African continent and in South Africa. Childhood experiences related to abuse, alcohol use, and criminal activities in the household and community has been associated with an increased risk for violence perpetration in adulthood. Less is known about sexual violence perpetration, especially in the South African context. In this study, the experiences of incarcerated male perpetrators of rape in South Africa are investigated along with the collective social context and individual childhood experiences that potentially contribute to rape perpetration. Eighteen male perpetrators of rape who were inmates at Westville Correctional Services in KwaZulu Natal, South Africa, were interviewed. The semi-structured in-depth qualitative interviews were transcribed, coded and annotated using an interpretive paradigm and thematic analysis approach. Five main themes emerged from the research and included 1. childhood trauma and adverse events, e.g., an absent father, being raised without parents, exposure to criminal or violent behavior, physical abuse, sexual abuse and poverty, 2. understanding rape, e.g., rape as sex by force and without consent, rape as a violent act, rape as sex with a minor, myths about rape 3. substance abuse, e.g., history of alcohol and drug use, and intoxication during rape perpetration, 4. gender roles and avoiding responsibility, e.g., victim blaming, rape as male prerogative, transactional sex, being framed or set-up, ignoring an ancestral call and 5. recidivism. The findings revealed that all rape perpetrators were exposed to at least one childhood trauma type. Family and community violence and criminality was common. Most participants avoided taking responsibility for their actions and blamed the victim and recidivism/prior convictions were often reported. The findings demonstrate the complex personality dynamic involved in the cycle of abuse and the evolution of criminal behavior, starting as a victim and ending as a perpetrator. The findings also highlight the need for interventions aimed at reducing childhood trauma exposure and improving the social and relational context of those at risk for childhood neglect and abuse.

Disclosures: L. Qulu: None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.08/K11

Topic: F.03. Stress and the Brain

Support: NIMH 1R01 MH117459
R01 NS045193
R01 MH128776
U19 NS104648

Title: Different early life adversity paradigms have disparate effects on maternal care, developmental social recognition, and neuronal activation

Authors: *V. BAPAT, R. C. WATERS, S. R. JANARTHANAN, L. A. LYNCH, S. S. WANG, E. GOULD;
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Abstract: In humans, childhood maltreatment has different effects on social recognition abilities depending on the type of maltreatment. In previous studies, we found different effects on social behavior in adults after two early life adversity mouse paradigms. Both maternal separation with early weaning (MSEW), a model of maternal deprivation, and limited bedding and nesting (LBN), a model of scarce resources, diminished social recognition but only LBN reduced investigation of novel mice. In adulthood, social dysfunction was only noted in male, but not female, MSEW and LBN mice. To explore these differential effects further, we carried out a series of experiments investigating maternal care behavior, neuronal activation patterns, and social behavior. We found that MSEW mothers spent more time on the nest (excluding the separation period) than control mothers, and that LBN mothers exhibited fragmented care in having a greater frequency of nest entrances/exits and shorter bouts on the nest compared to control and MSEW mothers. Next, we examined brain wide activation patterns by clearing pup brains using the iDISCO+ method, immunolabeling of c-Fos, and acquiring cellular resolution light sheet imaging volumes during the MSEW and LBN manipulations on postnatal day 7. We found different patterns of activation between the early life adversity paradigms with MSEW pups exhibiting less neuronal activation in the parietal, which includes somatosensory cortex, compared to control and LBN pups. LBN pups had greater activation in the pallial amygdala than control and MSEW pups. Both MSEW and LBN mice showed diminished activation in hippocampal regions compared to controls. Lastly, we explored the emergence of social recognition deficits in pups after MSEW and LBN. We found that both males and females showed social recognition impairments prior to puberty with MSEW mice exhibiting higher levels of social investigation than control-reared mice but no evidence of social discrimination. LBN mice showed lower levels of social investigation with no discrimination between social

stimuli. After puberty MSEW and LBN males remained impaired in social discrimination, but females showed complete recovery and normalization of this behavioral function. These findings suggest that maternal care differences induced by different early life adversity paradigms activate different brain regions and produce disparate sex-dependent trajectories of social recognition development. Future studies will investigate brain activation patterns at different ages, circuitry underlying differential effects of MSEW and LBN, as well as pubertal mechanisms of recovery from early life adversity.

Disclosures: V. Bapat: None. **R.C. Waters:** None. **S.R. Janarthanan:** None. **L.A. Lynch:** None. **S.S. Wang:** None. **E. Gould:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.09/K12

Topic: F.03. Stress and the Brain

Title: Assessment of Anxiety Behavior by Maternal Separation in Male Mice Exposed to Mozart´s K448 Sonata

Authors: *E. MARIANO[1], A. CARVALHO RIBEIRO[1], C. SARTORI[2], G. NEVES[1]; [1]Faculdade de Medicina de Itajubá, Itajubá, Brazil; [2]Campinas State Univ. - UNICAMP, Campinas, Brazil

Abstract: The stress can be defined as a fundamental adaptive response of the organism to deal with everyday situations. The exposure to stress in the early life, such as maternal separation, can generate behavioral changes in individuals, such as anxiety disorders. With the aim of attenuating anxious symptoms, the possible effects of music therapy have been addressed in the reconfiguration of neural connections by previous studies. Thus, we aimed to investigate the effects of Mozart's Sonata K.448 on animals with anxious behavior caused by maternal separation. For this purpose, we formed 6 experimental couples with C57BI/6JUniB mice with 9 weeks of age. These were separated into: **Stress (S) -** offspring subjected to maternal separation - and **No Stress (NS) -** offspring not subjected to stress. After birth, the selected offspring underwent the maternal separation stress protocol on the 1st postnatal day, during the light-dark cycle of the mice, starting at 8 pm and ending at 11 pm, for 14 consecutive days. On the 21st day, we performed the weaning of the offspring, separating the males into their respective experimental groups. At 9 weeks of age, we conducted the musical exposure. The experimental groups (n=10 per group): **Stress/K448/Male (S/K448/M) -** Males subjected to stress and exposed to Sonata K448 of Mozart. **Stress/Environment/Male (S/E/M) -** Males subjected to stress, and in ambient sound. **No stress/Environment/Male (NE/E/M) -** Unstressed males, and in ambient sound. **No stress/K448/Male (NE/K448/M) -** Male without stress, exposed to Sonata K448. The **Stress (S/K448/M)** and **No Stress (NE/K448/M)** groups received the Sonata K448 of Mozart, from 9 pm to 7 am, in specific cabinets for this procedure. At the end of that period, they

returned to the standard cabinet. Finally, an open field test was performed to verify the presence of anxious attitude, in which the time spent in the central and lateral quadrants, along with hearing behavior was evaluated. The sessions were recorded in videos that were later analyzed, and then these mice underwent euthanasia, and their brains were removed and frozen in dry ice and stored at -80°C. For data analysis, we used the two-way ANOVA statistical test, and after, the Tukey's multiple comparisons post-test, with no statistically significant difference found between the experimental groups ($p>0.05$). Therefore, there was no anxious behavior generated by the maternal separation protocol in the analyzed test, and the music did not demonstrate significant impact on altering the behavior of the mice.

Disclosures: E. Mariano: None. **A. Carvalho Ribeiro:** None. **C. Sartori:** None. **G. Neves:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.10/K13

Topic: F.03. Stress and the Brain

Support: NIGMS SC1GM144190
Texas Woman's University Research Enhancement Program

Title: The effects of early life stress on stress responses in POMC-Cre MeCP2 knockout mice

Authors: H. RANDEL[1], P. FRAYRE[2], S. VASQUEZ[1], *E. NA[3];
[1]Texas Woman's Univ., Denton, TX; [2]Biol., Texas Women's Univ., Denton, TX; [3]Texas Woman's Univ., Denton, TX

Abstract: Methyl-CpG binding protein 2 (MeCP2) is a neuroepigenetic factor, implicated in the pathophysiology of obesity. Previous work has shown that forebrain knockout (KO) of MeCP2 leads to an overweight phenotype in mice given chronic exposure to a high fat diet. Our lab has recently shown that knocking out MeCP2 specifically in pro-opiomelanocortin (POMC) neurons of the hypothalamus also produces an overweight phenotype, as well as increased plasma corticosterone levels - a stress hormone that can be detrimental when chronically elevated. Based on these data, we sought to determine if POMC-Cre MeCP2 KO mice were more sensitive to the effects of early life stress (ELS) using a mouse model of maternal separation. Behavioral tests for depression and anxiety were used to evaluate the effects of ELS on KO and wildtype (WT) mice. Hormones implicated in stress responses, including plasma corticosterone, adrenocorticotropic hormone (ACTH), and corticotropin releasing hormone (CRH), as well as levels of hippocampal brain derived neurotrophic factor (BDNF), a protein implicated in neuronal health, were quantified utilizing enzyme-linked immunosorbent assays (ELISAs). Our current data suggest that ELS exacerbates stress in POMC-Cre MeCP2 KO mice relative to WT mice, and that MeCP2 may be a candidate mechanism underlying stress regulation in POMC-specific neurons.

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

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

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Program #/Poster #: PSTR471.11/K14

Topic: F.03. Stress and the Brain

Support: NIH NIGMS P20GM103423

Title: A sex-specific assay of adversity-induced hypervigilance and its attenuation by ketamine: roles for parvalbumin, DNA methylation, and pubertal estrogens in rats

Authors: Y. A. PENA[1], C. J. SCOTT[1], N. FENG[1], S. M. BONAUTO[1], E. S. NOEL[1], S. N. ELLIS[1], *J. A. HONEYCUTT[2];
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Abstract: A history of early life adversity (ELA) - including childhood neglect - significantly increases the risk of developing later-life disorders, including anxiety and post-traumatic stress disorder. These outcomes also have higher prevalence in women, making it important to evaluate the role of sex in adversity outcomes. In humans, and in animal models, ELA leads to altered processing of affective information, including potential threat, which manifests as contextually inappropriate hypervigilance and anxiety-like behavior. However, we lack robust assays in rats that are translationally relevant to human experiences. Rat 22kHz ultrasonic vocalizations (USVs) communicate potential threat to conspecifics and may serve as a rat analogue to fearful face presentation in humans. When presented with 22kHz USV playback, we have observed that juvenile ELA female rats show increased anxiety-like behavior which is associated with decreased prefrontal cortex (PFC) inhibitory tone measured through parvalbumin (PV) cell recruitment, compared to control-reared and male counterparts. However, as young adults, ELA females lose this behavioral phenotype and instead show an increase in hypervigilant-like active avoidance during 22kHz playback. We show that this phenotype is reversed in ELA females following an acute therapeutic dose of 15mg/kg ketamine one week prior to testing. To investigate whether behavioral hypervigilance in ELA females was associated with pubertal estrogens, a separate study conducted ovariectomies (OVX) or sham surgeries in control and ELA reared females. Like ketamine treatment, OVX also reduced hypervigilance in response to 22kHz USV playback in ELA females, suggesting a role for pubertal estrogens in mediating ELA's behavioral effects. To determine whether behavioral outcomes were related to epigenomic changes within the PFC, especially in PV neurons which are well positioned to gate behavioral output, another cohort of rats was evaluated for changes in PV and PV-specific DNA methylation (via 5-methylcytosine; 5mC). Juvenile ELA males and females show a more adult-like PV and 5mC phenotype, though there were no significant effects of ELA observed in young adults. However, young adult ELA females showed a modest reduction in 5mC intensity within PV cells following acute ketamine treatment. In sum, we present compelling evidence for: 1) the

translational promise and sensitivity of 22kHz USV playback to assess hypervigilant behaviors in rats; 2) the impact of pubertal estrogens in mediating ELA's behavioral outcomes; 3) a role for PV methylation in ELA's pathophysiology; and 4) ketamine's ability to reverse ELA outcomes in female rats.

Disclosures: Y.A. Pena: None. **C.J. Scott:** None. **N. Feng:** None. **S.M. Bonauto:** None. **E.S. Noel:** None. **S.N. Ellis:** None. **J.A. Honeycutt:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.12/K15

Topic: F.03. Stress and the Brain

Support: Seaver Foundation Fellowship

Title: Comparing changes in social behavior following juvenile and chronic social isolation

Authors: *M. KIM[1], M. BARBIER[2], H. HARONY-NICOLAS[3];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Psychiatry, Mount Sinai Sch. of Med., New York, NY; [3]Psychiatry/Neuroscience, Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Social interactions during development are crucial for establishing adult social behavior. An important facet of social behavior is the rewarding properties of social interaction, and in both humans and animals, sensitivity to social reward and social interactions changes during adolescence, and stressors during this phase, such as social isolation (SI), can adversely affect behavior long-term. However, many previous studies investigating the impact of juvenile social isolation (jSI) do not limit isolation to specific developmental phases but rather, extend isolation into adulthood, making it difficult to discern if there are specific critical periods during which social isolation produces long-term consequences on social behavior. Additionally, some studies test changes in behavior while animals continue to be housed in isolation, making it unclear if behavioral changes observed in tested animals are indeed long-term consequences of social deprivation or effects resulting from the stressor of isolation housing. For this purpose, we use a social preference assay and a social vs. food task to assess social behavior following jSI, where rats are isolated during adolescence then resocialized prior to behavioral testing in adulthood, and chronic social isolation (cSI) where rats are isolated beginning in adolescence until behavioral testing in adulthood. We found male and female rats raised in jSI (n = 26) do not show significant differences in social preference or social reward-seeking behavior compared to GH rats (n = 28). However, compared to GH rats (n = 17), cSI rats (n = 20) display increased investigation of the social stimulus during the social vs. food task at satiety and after 48 hours of food deprivation (paired t-test, GH rats, $t_{(16)} = 0.630$, $p = 0.538$; jSI rats, $t_{(19)} = 3.486$, $p < 0.005$). Our findings indicate that compared to GH rats, cSI rats display increased preference for a social stimulus when presented with a competing non-social stimulus while jSI rats show no

differences in social preference. These results may suggest that while cSI produces deficits in social behavior, the experience of resocialization following SI may ameliorate possible social deficits precipitated by jSI. Ongoing behavioral experiments will better elucidate whether there is a specific critical period during development in which SI produces persistent deficits in social behavior.

Disclosures: M. Kim: None. **M. Barbier:** None. **H. Harony-Nicolas:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.13/K16

Topic: F.03. Stress and the Brain

Title: The relationship between fatigue level, positive and negative affect among university students.

Authors: *D. BALGANSUREN[1], B. BAYANMUNKH[2], N.-E. OTGON[1], T. JADAMBA[3], C. ERDENEBAATAR[4], N. BAT-[5], L. BATERDENE[6], B. KHANGALSUREN[7], S. LKHAGVASUREN[6], B. LKHAGVASUREN[1];
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Abstract: Chronic fatigue is a pervasive concern among university students, impacting various facets of their academic and personal lives. This study examines fatigue levels, demographic factors, and affect among 487 university students in Mongolia. With a mean age of 20.56 years (SD = 2.01), the participants were 263 females and 224 men from the University of International Affairs, Mongolia (N = 202) and the Mongolian National University of Education (N = 285). The Chalder Fatigue Scale (CFQ) was used to measure fatigue, and the results showed mean scores for mental (M = 12, SD = 5.8), physical (M = 11.9, SD = 4.6), and overall (M = 17.81, SD = 6.8) fatigue. Notably, the maximum possible score on the CFQ is 33, yet our average score is less than half of this criterion. There were significant differences between genders in physical and mental fatigue variables, as well as overall scores ($p < .05$). Additionally, differences were observed across two universities ($p < .05$). Using one-way ANOVA, differences were also found between university grades, with significant variations among freshmen, sophomores, juniors, and seniors ($p < .05$). Participants also filled out the Positive and Negative Affect Scale (PANAS), which resulted in mean scores for positive affect of 33.2 (SD = 6.05) and negative affect of 27.4 (SD = 6.7). Significant differences were found between genders and universities for both negative and positive affect factors ($p < .05$), while no differences were observed across university years. Correlation analyses revealed associations between fatigue and affect,

indicating positive correlations with negative affect and negative associations with positive affect. While our study provides insight into average fatigue levels among Mongolian students, future research could benefit from employing more precise instruments to capture the complexities of fatigue and its effects on the academic and psychological experiences.

Disclosures: D. Balgansuren: None. **B. Bayanmunkh:** None. **N. Otgon:** None. **T. Jadamba:** None. **C. Erdenebaatar:** None. **N. Bat-:** None. **L. Baterdene:** None. **B. Khangalsuren:** None. **S. Lkhagvasuren:** None. **B. Lkhagvasuren:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.14/K17

Topic: F.03. Stress and the Brain

Support: GRK 2350

Title: Daily-life and neural correlates of social exclusion in healthy individuals with adverse childhood experiences

Authors: *N. ROYCHOUDHURY, Y. LIN, O. BERHE, J. ANDOH, A. S. MEYER-LINDENBERG, H. TOST;
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Abstract: Adverse childhood experiences (ACE) are associated with altered social behaviors in later life, and have long term effects on social affective brain circuits. Social interactions may trigger threat vigilance and stress related behaviors for ACE-exposed adults. Prior literature has found differences in neural responses during social stress tasks in ACE-exposed adults when compared to healthy controls. We aim to explore risk and resilience factors in the social environment such as perceived exclusion, and how these are associated with ACE. We further examine neural responses relating to social exclusion, and their relationship with these environmental factors. 51 healthy individuals (39 women) aged 19-53 (M=32.78, SD=10.21) with mild to moderate ACE exposure were recruited as a community-based cohort. Data collection is ongoing with the final sample size set at 60 participants. The study has a randomized, multimodal, crossover design. Participants responded to Ecological Momentary Assessment (EMA) prompts over two weeks, of which one week required them to additionally engage in Ecological Momentary Strategies (EMS) based on principles of attention bias modification. Two fMRI scans with the Cyberball, a social ostracism paradigm, were administered at the end of the EMA and EMS weeks to ascertain the differences in perceived social exclusion and the protective effects of the EMS depending on ACE. Finally, the participants also completed various sociodemographic and psychological questionnaires. Mixed effects analyses showed higher childhood trauma to be associated with greater perceived

exclusion in both weeks (p=0.03). However, perceived exclusion was lower in the EMS week, and decreased further with every per unit increase in childhood trauma, which may indicate social buffering. This effect also held for perceived stress (p=0.01). Further fMRI results for Cyberball will be presented at the SFN conference, with the regions of interest including the insula, and parts of the ACC and PFC. We hypothesize that there is a relationship between these neural correlates and EMA measures, and that this relationship is moderated by ACE.

Disclosures: N. Roychoudhury: None. **Y. Lin:** None. **O. Berhe:** None. **J. Andoh:** None. **A.S. Meyer-Lindenberg:** None. **H. Tost:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.15/K18

Topic: F.03. Stress and the Brain

Title: Effects of Social Isolation Stress on Cognitive Performance and Alleviation through Environmental Enrichment

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Abstract: Previously, we used mice as a model to examine the effects of stress caused by social isolation in childhood on memory and learning abilities. We found that mice who were socially isolated had significantly lower memory and learning abilities in the maze learning test. Therefore, in this study, we investigated the effects of social isolation during childhood in further detail, including its impact on activity levels, and examined whether environmental enrichment could alleviate social isolation-induced stress. Understanding the effects of environmental enrichment can underscore the importance of play, which is the most familiar form of activity during childhood.Male C57BL/6N mice were used in the study. Anxiety and stress levels were assessed through an open-field experiment and an elevated plus maze test, whereas memory and learning abilities were evaluated via a seven-route maze experiment. Three-week-old mice were procured and divided into two groups: an isolated group and a group-housed group. Each of these groups was further subdivided based on the presence or absence of environmental enrichment, which was maintained until the end of the experiment (at 11 weeks of age). Environmental enrichment was provided in the form of a running wheel with a playful element. Behavioral experiments were conducted after 1 week (at 4 weeks of age) and 1 month (at 7 weeks of age) to compare the effectsof each environment before and after exposure. Additionally, the activity level and body temperature throughout the experimental period were monitored using a subcutaneouslyimplanted measuring device.No significant differences were observed among the four groups in terms of changes in the body temperature of the mice or the outcomes of the open-field experiments and elevated plus maze test. However, consistent with the findings of previous studies, mice subjected to social isolation during childhood tended to

exhibit delayed learning in the seven-route maze compared with their counterparts. This tendency may be attributed to their experience of social isolation:growing up in an environment devoid of interaction and response from others, which could lead to a lack of motivation for learning. These findings suggest that maintaining motivation for mazelearning proved challenging for the isolated mice.Conversely, mice raised in the presence of environmental enrichment, regardless of whether they were housed in a solitary environment or in a group, tended to be more active than those raised without environmental enrichment. This suggests that environmental enrichment alleviates social isolation stress.

Disclosures: M. Morita: None. **H. Kawaguchi:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.16/K19

Topic: F.03. Stress and the Brain

Support: NSF Grant DBI: 2208822
R01 Grant DA056534

Title: Early life adversity exacerbates adult impulsivity: insights from neonatal predator exposure in rats.

Authors: *K. MESAPE[1], M. STRICKLIN[2], N. BROWN[2], E. ANDREWS[2], S. B. FLORESCO[3], D. A. BANGASSER[4], A. CUARENTA[5];
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Abstract: Experiencing early life adversity can increase the risk of developing neuropsychiatric disorders such as substance use disorders, that are characterized by impairments in decision-making. However, the effects of early adversity on impulsive behavior in adulthood remain understudied. Here we addressed this gap by inducing early adversity in rats with predator odor exposure (POE) in the neonatal period and evaluating impulsive choice in adulthood using the delay discounting task. Specifically, Sprague Dawley rat pups were exposed to bobcat, rat, and ferret odors for 5 minutes each on postnatal days (PND) 1,2 and 3 respectively. Control rats were handled similarly but only exposed to clean bedding. After this brief early life stressor, rats from both groups were raised in standard conditions until adulthood. Beginning at PND 100, male and female rats were trained on the delayed discounting task, where they could either press the low reward lever to obtain 1 pellet immediately or the high reward lever to obtain 4 pellets after a delay (0, 15, 30, and 45 seconds over 4 trials respectively). Our preliminary data demonstrates that POE-exposed rats pressed for the immediate/smaller reward, forgoing the delayed/larger reward, more than controls. This result suggests that POE causes long-lasting changes in

impulsivity that persist into adulthood. Future research will focus on determining the underlying neurobiological changes induced by POE that mediate the increase in impulsivity.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.17/K20

Topic: F.03. Stress and the Brain

Support: NIMH R01 MH130825

Title: High levels of maternal fragmentation do not impair attachment behavior in a mouse model of early life adversity

Authors: *Z. A. MACDOWELL KASWAN[1], A. HERRERIAS[2], N. PAJARILLO[2], G. MURTY[3], A. KAFFMAN[1];
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Abstract: Inconsistent and erratic parenting leads to insecure attachment, characterized by abnormal response to parental cues. According to the attachment theory, these early deficits contribute to long-term emotional dysregulation, enhanced threat detection, and abnormal social behavior. Elucidating the mechanisms by which erratic parenting impairs the development of normal attachment behavior is difficult to do in humans and only a few studies have examined this issue in rats. To the best of our knowledge, no studies have investigated this question in mice or used long-term home-cage monitoring to assess maternal care and relate these changes to attachment behavior and social abnormalities later in life. Here, we used the Noldus Phenotyper to rigorously assess the effects of limited bedding (LB) on maternal behavior from post-natal day 2 (P2) to P7. This approach allows us to continuously record and assess total locomotor activity, time in nest, and frequency of entering and exiting the nest (maternal fragmentation) over a five-day period in the home cage without experimenter interference. A within-litter design was used to correlate levels of maternal fragmentation with frequency of ultrasonic vocalizations (USVs) and maternal buffering at P8. Similar approaches were used to assess the effects of maternal fragmentation on exploration in the open field test (OFT) and maternal preference at P18. We found that dams raising litters under LB conditions spent equivalent time on the nest compared to those in control (CTL) condition but showed significantly higher levels of fragmentation. Higher levels of maternal fragmentation were more prominent during the dark phase with significant individual variations across different LB dams. LB reduced pup body weight at P8, but this effect was not significantly correlated with levels of maternal fragmentation. P8, LB pups had fewer USVs during isolation than CTL pups but exhibited similar reduction in USVs in

response to anesthetized adult female conspecific. At P18, LB pups spent less time in the center of the open field test, but had normal maternal preference. No significant correlations were found between levels of maternal fragmentation and distress vocalizations at P8, maternal buffering at P8, or maternal preference at P18. These findings suggest that high levels of maternal fragmentation from P2-7 is not sufficient to impair maternal attachment.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

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Topic: F.03. Stress and the Brain

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NIH Grant MH123153 to EDL

Title: Unsupervised segmentation of behavioral outputs in control and early-life stressed mice

Authors: *M. BOMPOLAKI[1,2], L. KING[3], S. A. DOMINGUEZ[1,2], T. LAGO[4], J. NYE[5], E. D. LEONARDO[6,7], A. DRANOVSKY[6,7];
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Abstract: A staggering proportion of the population experiences adversity during childhood, including inadequate caregiving, poverty, exposure to natural disasters or other traumatic events. These experiences, even if short-lived, occur during sensitive developmental periods and have pervasive consequences for mental health. The limited nesting and bedding paradigm (LBN) emulates fragmented care due to limited resources and has been used to study the extensive effects of early life stress (ELS) in rodents. LBN has been used across numerous labs with robust effects on brain development, but with mixed findings in several behavioral tasks. These shortcomings have been attributed to limited number of animals and inconsistencies of behavior scoring. Recent advances on computer vision and the development of methodologies for unbiased labeling have revolutionized the field of behavioral neuroscience providing the opportunity to study multiple behaviors in large cohorts of animals eliminating the inherent variability of human scoring. Here, we tested two separate cohorts of mice aged 5-6 or 12-18 months across 6 different behavioral tasks to probe diverse constructs including anxiety,

exploration, working memory and social memory. The tasks included elevated plus maze, open field, spontaneous alternations, spontaneous object location, sociability, and social memory. All videos were recorded from a bottom view to maximize consistency and presence of all tracked body parts. All videos were processed using the deeplabcut (DLC) pose estimation platform. Time series of body part x-y locations were processed to programmatically determine validated standard task measures. Additionally, the DLC output was clustered using unsupervised dimensionality reduction algorithms B-SOiD and CEBRA to identify behavior domains from each task and how their representations differ between control and ELS animals and across age. Our extensive data set enabled us to unambiguously validate ELS effects across behavioral tasks including determining effect sizes. We were also able to determine the role of the nest size and pre-weaning weights on behavior. Furthermore, unsupervised clustering revealed differences in the animals' behavior that were previously inaccessible. Overall, this work further solidifies and extends our understanding of the enduring effects of ELS and highlights the value of establishing data-driven pipelines to maximize reproducibility in behavioral neuroscience research.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.19/K22

Topic: F.03. Stress and the Brain

Support: NIEHS ES 100221

Title: The Effect of Prenatal Corticosterone Exposure on Hippocampal Area CA2 Development and Social Behavior

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Abstract: In humans, prenatal stress and, similarly, exposure to glucocorticoids in utero is known to change the structure and connectivity of brain regions including the hippocampus (Ilg et al., 2018; Van den Bergh et al., 2020). Prenatal stress also increases one's risk of developing a neurodevelopmental disorder—like autism, ADHD, bipolar disorder, or schizophrenia—that are often marked by social deficits. The hippocampus expresses both the glucocorticoid receptor (GR; in area CA1) and the mineralocorticoid receptor (MR; highest in area CA2 and dentate gryus). The hippocampus is particularly enriched with MR early in embryonic development (Kretz, et al., 2001), long before GRs come online, suggesting that MRs could be the primary target of glucocorticoids like corticosterone (CORT) in the prenatal brain. Previously, our lab found that a 7-day treatment of CORT via pellet implant in adult mice reduces CA2 expression

of MR and the CA2 marker RGS14 and that MR knockout disrupts CA2's molecular profile. Thus, a remaining question is how exposure to CORT early in development influences hippocampal development and its related behaviors. We hypothesize that early life stress—through CORT acting on MRs — regulates CA2's molecular profile and role in behavior. To isolate the specific effects of CORT from other hormones and neurotransmitters released during chronic stress, we treated pregnant mouse dams from gestational day 9.5 to littering (10 days) with either a 1% ethanol vehicle or a high (50 µg/ml) or low (35 µg/ml) concentration of CORT via the homecage drinking water. Mass spectrometry on newborn pup brains showed that CORT was indeed elevated in the high CORT treated animals. Pups underwent a maternal preference test (MPT) at postnatal days (P) 14, 21, and 35 to identify potential differences in early social preference (Laham et al., 2021). Between P60 and P70, pups underwent additional testing with open field, novel object recognition, elevated plus maze, and three chamber social recognition. Animals were euthanized at the timepoints of interest and their brains flash-frozen and cryosectioned for subsequent staining and in situ hybridization. The researcher has been blind to treatment during behavioral testing, staining, and data analysis. Thus far, CORT does not appear to have effect in the MPT, as no differences between groups were found between the three blinded treatment groups. Staining and additional behavioral testing in adults is ongoing and should reveal whether manipulation of glucocorticoid levels—potentially via MR activity— has effects on CA2 in a way that impacts social behavior.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.20/K23

Topic: F.03. Stress and the Brain

Title: Sex differences in the effects of prenatal stress on social behavior

Authors: *C. LEWIS[1], T. BUCK[2], D. J. RADEMACHER[1], M. MCCARTHY[1], M. S. SODHI[2]; [2]Mol. Pharmacol. and Neurosci., [1]Loyola Univ. Chicago, Maywood, IL

Abstract: Prenatal stress (PRS) increases the risk of disorders associated with impaired socialization, such as schizophrenia and autism spectrum disorders, in males but not females. These are lifelong disorders, and treatments have poor efficacy. Pregnant mice were exposed to 30 minutes of restraint stress twice daily during weeks 2 and 3 of gestation. In adulthood, male and female offspring were tested for social interaction and social memory using the 3-chamber social interaction (SI) test. Initial results found a significant effect of stress ($F1, 11 = 4.869$, $p = 0.050$). Post-hoc analysis revealed a significant difference between non-stressed (NS) and PRS males ($p = 0.048$) where NS males spent more time in the interaction chamber (207.8 s ± 71.57) compared to PRS males (102.3 s ± 67.09). To understand the sex differences underlying the

effects of prenatal stress, we are measuring the synaptic expression of AMPA-type glutamate receptors using immunohistochemistry in the CA2 of the dorsal hippocampus, which is associated with social behavior, in male and female mice. We are also using neuronal tracing to measure synaptic maturation and to test if altered synaptic expression of AMPARs in CA2 leads to impaired synaptic density and social behavior associated with prenatal stress. Understanding the mechanisms associated with these findings may provide novel targets for developing more efficacious drugs to treat disorders with impaired social behavior.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.21/K24

Topic: F.03. Stress and the Brain

Title: Comparison of cardiovascular reactivity and catecholamines, before and after, induced mental stress.

Authors: *J.-I. SÁNCHEZ-DOLORES[1], A. OSORIO-ESPINOZA[2], A.-L. GONZÁLEZ-NABOR[1], C. PLIEGO VILLANUEVA[3], I. PLIEGO-PLIEGO[4];
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Abstract: One of the main health problems of recent decades worldwide is chronic stress, generated by multiple factors. This type of stress creates various consequences that affect health and an imbalance between work and personal life.On the other hand, chronic degenerative diseases increase year after year, in our country we occupy the first places worldwide in diabetes, obesity, and high blood pressure, one of the most frequent chronic diseases, according to data from the National Institute of Statistics and Geography (INEGI) of 2020, indicate that 24.9 percent of men and 26.1 percent of women suffer from this disease, which causes nearly 50 thousand deaths each year. These pathologies, together with chronic stress, can deteriorate health and quality of life.An observational, prospective, and longitudinal study was carried out; a perceived stress scale was applied and, measurements of blood pressure, heart rate, and measurement of catecholamines in blood were carried out, using ELISA, subsequently induction of mental stress was carried out, applying the Stroop test, and after the test, all the measurements mentioned above, were carried out again. Statistical analysis was performed using the T-student paired test, with significance set at p=0.05.
The sample was 44 participants from a higher education center identified as having moderate and high perceived stress. Cardiovascular reactivity (blood pressure and heart rate) was measured before and after applying a mental stressor using the Stroop Test. Regarding the measurement of

blood pressure, a statistically significant difference was found, with a value of P = 0.0123, between the measurement before and after the application of the Stroop Test. In the measurement of heart rate, a statistically significant difference was also found, with a value of P = 0.0005, in terms of adrenaline level, a statistically significant test was found, with a value of P = 0.0074.

Disclosures: J. Sánchez-Dolores: None. **A. Osorio-Espinoza:** None. **A. González-Nabor:** None. **C. Pliego Villanueva:** None. **I. Pliego-pliego:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.22/K25

Topic: F.03. Stress and the Brain

Title: Generational Effects of Chronic Stress in Mice

Authors: *C. HARTLESS[1], M. N. COOK[2];
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Abstract: Stress can affect neurobehavioral systems in the individual that may have generational effects on behavior. In humans, children from parents with a history of stress have a higher risk for developing anxiety and depression. Perinatal stress alters early-life development, however the effects of stress, prior to conception, are not well understood. In this project, C57BL/6J and DBA2/J mice experienced 4-weeks of chronic unpredictable stress (CUS). Control (BCON) and CUS (BCUS) breeders were established one week after exposure to stress. To evaluate maternal care, pup retrieval, nest quality, litter size, and pup weights were compared. CUS did not affect litter size or litter weight. CUS decreased nest quality in D2, but not B6 mice. CUS decreased pup retrieval time but not latency to first contact. Offspring were weaned at postnatal day (PND) 21 and began CUS at PND35. After CUS, control (C) and stressed (S) offspring from BCON and BCUS breeders were assessed in the Zero Maze (ZM), Open Field (OF), Light/Dark (LD), and Sucrose Preference (SP) tasks. For B6 male mice in the ZM, S-BCON, C-BCUS, and S-BCUS spent less time in open quadrants than the C-BCON group. For B6 females, C-BCON and S-BCON mice did not differ, however BCUS spent more time in the open than the S-BCUS mice. In the D2 mice, S-BCON spent more time in the center than BCON, BCUS and S-BCUS groups. For B6 mice in the OF, S-BCON spent less time in the center than C-BCON, C-BCUS, and S-BCUS groups. In D2 mice, BCUS, but not S-BCUS spent less time in the center when compared to the C-BCON group. In LD, S-BCON and S-BCUS spent less time in the lit compartment than controls. In D2 mice, S-BCUS mice spent more time in the lit compartment when compared to C-BCON, S-BCON, and C-BCUS groups. For SP, B6 mice in S-BCON, C-BCUS, and S-BCUS groups consumed less sucrose than C-BCON mice. In D2 mice, S-BCON and C-BCUS groups consumed less sucrose, however S-BCUS consumption was not different from the C-BCON group. Evidence suggests that chronic stress contributes to changes in behavior that are sex and

strain dependent. These effects show how gene and environmental factors can differentially affect vulnerability to chronic stress within and across generations.

Disclosures: C. Hartless: None. **M.N. Cook:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.23/K26

Topic: F.03. Stress and the Brain

Support: DK135871
MH129970
NS088555
NS126279

Title: Early-life bladder inflammation in the female mouse: later-life consequence for voiding and anxiety-like behavior

Authors: A. J. EISCH[1], N. BABIKER[2], S. BUTLER[2], L. PEREZ CLASSE[2], T. GODFREY-ANDRADE[5], G. BANCROFT[2], *N. S. JOHNSON[6], J. FESI[3], S. A. ZDERIC[4], S. YUN[7]; [1]Anesth & Crit Care and Neurosci, UPenn & CHOP, Swarthmore, PA; [3]Urology, [4]Pediatric Urology, [2]Children's Hosp. of Philadelphia, Philadelphia, PA; [5]Univ. of Pennsylvania, Wesley Chapel, FL; [6]Dept. of Neurosci., Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; [7]Anesthesiol. and Critical Care, CHOP, Swarthmore, PA

Abstract: Lower Urinary Tract Symptoms (LUTS) - urgent, frequent voids of small volume - are prevalent at all ages. LUTS can be induced in rodents via a bladder inflammation model, and such systemic inflammation can result in neuropsychiatric-like symptoms. Understanding the connection between systemic inflammation and LUTS is critical for the fields of urology as well as neuroscience, and it may indicate novel treatments and help explain how peripheral organ status influences brain function. Notably, few studies have examined if early-life bladder inflammation can induce later-life LUTS. This is a critical knowledge gap; for example, our clinical data show early-life (<3 yo) urinary tract infection (UTI) is 4.4x more likely to result in later-life LUTS and anxiety. To fill this gap, we developed and characterized an early-life bladder inflammation mouse model using the most common rodent non-invasive (catheter-free) adult bladder inflammation model: injection of cyclophosphamide (CYP). Male and female C57BL/6J pups were given CYP (25 and 50mg/kg, s.c.) or saline (Sal) on postnatal day (P)7 and P10. One cohort (5 litters, male: n=5-6/group, female: 8-9/group) was used for a dose-response study and to collect P13 body weights and bladder brain mass index (BBMI). A second cohort was assessed for longitudinal voiding (UroVoid metabolic chamber, 2 days each at P50, P120, and P210), anxiety-like behavior testing (P60-67), and bladder muscle contractility and BBMI (P210). For body weight, at P13 50mg/kg—but not 25mg/kg—CYP mice weighed less than Sal.

BBMI was higher in both CYP groups and in both sexes vs. Sal mice, suggesting bladder inflammation. For voiding, 25mg/kg CYP mice had more voids and higher void frequency vs. Sal mice at both P50 (n=21-22/group) and P120 (n=12-14/group). For later-life BBMI, at P210 both CYP groups had higher BBMI vs. Sal mice (n=8-9/group). Mechanistically, although these data show early-life CYP-induced voiding dysfunction is persistent in later-life, P210 bladder muscle contractility was normal (n=8-9/group). Analysis of anxiety-like behaviors and brain-region inflammation is ongoing. These data begin to fill the gap on how early-life bladder inflammation influences later-life LUTS, with the goal of developing interventions.

Disclosures: A.J. Eisch: None. **N. Babiker:** None. **S. butler:** None. **L. Perez Classe:** None. **T. Godfrey-Andrade:** None. **G. Bancroft:** None. **N.S. Johnson:** None. **J. Fesi:** None. **S.A. Zderic:** None. **S. Yun:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.24/K27

Topic: F.03. Stress and the Brain

Title: Enriched maternal care combined with Sodium Propionate supplementation reverses outcome of inherited stress vulnerability in mice

Authors: *B. G. S. ROCHA[1], D. SUR[2], O. AGRANYONI[3], A. BAGAEV[1], R. A. ARAÚJO JUNIOR, Jr.[1], A. PINHASOV[1];
[1]Mol. Biol., Ariel Univ., Ariel, Israel; [2]Dermatol., Univ. of Wisconsin, Madison, Madison, WI; [3]Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: The gut-brain axis (GBA) is a bidirectional communication network between the gastrointestinal tract and the central nervous system, significantly impacting physiology and behavior. Using selectively bred mice exhibiting strong and stable features of social dominance (Dom) and social Submissiveness (Sub), we demonstrated that the proper activity of the GBA depends on inherited features of stress-coping abilities of the organism. We have previously demonstrated that Sub mice possess innate stress vulnerability accompanied by altered behavioral performances, age-dependent development of chronic inflammation, metabolic alterations, and reduced lifespan. Our recent findings reveal that compared with Dom mice, Sub mice show less diverse gut microbiota composition, reduced fecal short-chain fatty acids (SCFAs) levels, altered gut morphology, mucus production, and enhanced gut permeability. Furthermore, inborn stress vulnerability in Sub mothers is associated with a reduction in the abundance of *Lactobacillus reuteri* and a lack of increase in postpartum serum oxytocin, potentially leading to poor maternal care. Cross-fostering experiments, in which Sub pups were raised by Dom mothers (Sub/D), reversed the submissive endophenotype. Thus, Sub/D pups exhibited elevated hippocampal expression of DNMT3A at PND 7 and increased 5-mC levels at PND 21. Furthermore, adult Sub/D offspring exhibited increased sociability, induced

hippocampal glutamate and monoamine levels resembling the neurochemical profile of Dom mice. Sub/D offspring showed differences in their gut microbiota composition and colon length, as well as distinct gene expression patterns related to mucus production and tight junctions in the colon. Supplementation of the cross-fostered Sub/D with sodium propionate (SP) further improved behavioral and physiological parameters by means of a significant reduction in anxiety-like behavior, increased gut and colon lengths, as well as a reduction in intestinal permeability and goblet cell area. Thus, this study demonstrates that enriched maternal care coupled with the restoration of gut physiological function, may significantly improve the functionality of the GBA and prevent GBA-related metabolic and behavioral abnormalities later on in life.

Disclosures: B.G.S. Rocha: None. **D. Sur:** None. **O. Agranyoni:** None. **A. Bagaev:** None. **R.A. Araújo Junior:** None. **A. Pinhasov:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.25/K28

Topic: F.03. Stress and the Brain

Title: Maternal sodium propionate supplementation rescue from stress related metabolic and behavioral outcomes in offspring

Authors: *A. BAGAEV[1], D. SUR[2], O. AGRANYONI[3], B. ROCHA[1], S. NAVON-VENEZIA[1], A. PINHASOV[1];
[1]Mol. Biol., Ariel Univ., Ariel, Israel; [2]Dermatol., Univ. of Wisconsin, Madison, Madison, WI; [3]Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: The maternal gut microbiota shapes the offspring's intestinal microbiota from early postnatal stages, influencing their later-life metabolic, behavioral, and cognitive characteristics. Factors such as mode of delivery, nutrition, inflammation, exposure to drugs and toxins, as well as stress, can modulate the composition and diversity of maternal microbiota, consequently impacting the offspring's developmental trajectory. Using a selectively bred mouse model that exhibits stable behavior patterns of social dominance (Dom) and social submissiveness (Sub), coupled with inherited stress resiliency or vulnerability, respectively, we recently demonstrated that compared with Dom mice, Sub mice exhibit altered and less diverse gut microbiota (e.g. abundance of the critical bacteria genus *Lactobacillus*) composition from early infancy, accompanied by lower fecal levels of short-chain fatty acids (SCFA, butyrate, acetate, propionate), increased gut permeability, inflammation and metabolic alterations. In this study we explored whether sodium propionate (SP) supplementation (200 mM) to Sub dams during prenatal and postnatal periods could rescue the Sub mice phenotype. SP was administered via drinking water *ad libitum* from gestational day (GD) 0 and postnatal day (PND) 1. We found that in both experimental modes, SP supplementation either from GD 0 or PND 1 significantly

reduced Sub dams gut permeability, and elevated maternal behavior, as well as ameliorated anxiety-like behavior, improved short-term memory and sociability in Sub male offspring. These changes are accompanied by a significant reduction in inflammation and metabolic features. Thus, this study demonstrates that innate stress vulnerability-related behavioral changes may be compensated for by restoring gut physiology and preventing different metabolic and behavioral outcomes later in life. Metabolite supplementation, such as propionate during gestation and postpartum periods, may offer an exciting approach to the treatment of stress-related developmental abnormalities.

Disclosures: A. Bagaev: None. **D. Sur:** None. **O. Agranyoni:** None. **B. Rocha:** None. **S. Navon-Venezia:** None. **A. Pinhasov:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.26/K29

Topic: F.03. Stress and the Brain

Support: National Natural Science Foundation of China (81961128024)
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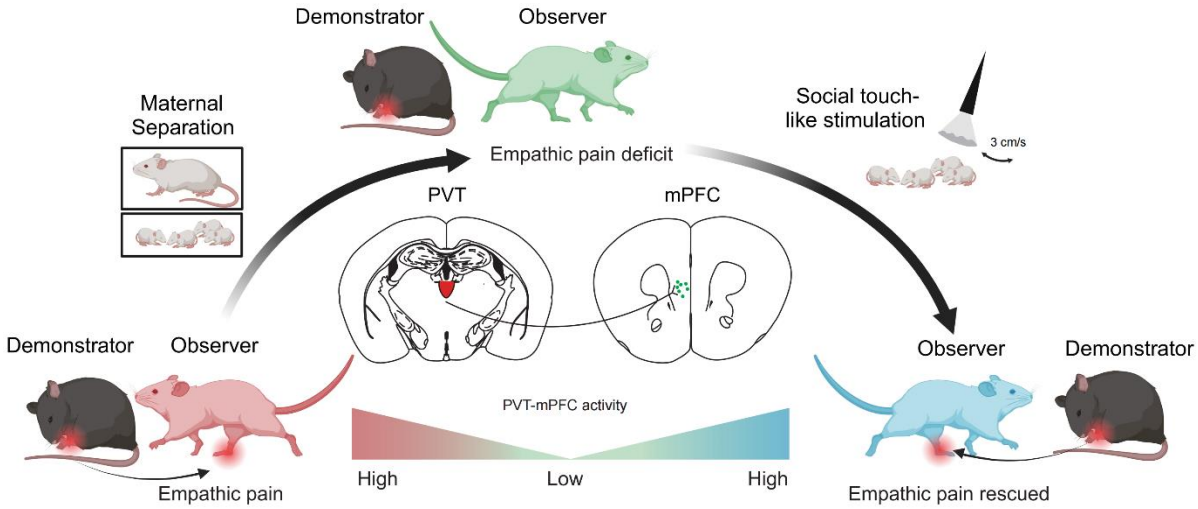
STI2030–Major Projects (2021ZD0203302)
National Natural Science Foundation of China (32170994)
Science and Technology Commission of Shanghai Municipality (18JC1420305)

Title: Pvt-mpfc circuit: a dual role in maternal separation-induced empathic pain deficits and recovery via social touch

Authors: *Z. ZHANG;
Shanghai Children's Med. Ctr. Affiliated to Shanghai Jiaotong Univ. Sch. of Med., Shanghai, China

Abstract: Empathy is defined as an evolutionary behavior of a subject associated with the ability to feel, recognize, understand and share the others' distressing states. It ranges from primitive forms such as mimicry and emotional contagion to high-level forms. Recent years have witnessed a gradual increase in the number of animal studies investigating neuronal and circuit mechanisms underlying the empathic contagious pain, one important type of emotional contagion. However, much less information is now available regarding the neurobiological substrates for the modulation of empathic pain by various external or internal factors. Early life stress, which includes various forms of child abuse and neglect, has repeatedly been shown to increase the risk to develop maladaptive behaviors in adulthood. Yet, whether and how early life adversity affects empathy-like behavioral performance remain poorly understood. In the present

study, we identified glutamate neurons of the paraventricular thalamus (PVT) and their specific projections to the medial prefrontal cortex (mPFC) as a key mediator of empathic contagious pain. Furthermore, we revealed a decreased activity as well as response of PVT neurons or PVT→mPFC circuit to socially transferred negative information in MS mice, thus blunting the social transfer of pain. Notably, chemogenetically increasing the PVT excitability or activating the PVT→mPFC projection significantly rescued MS-induced empathy pain deficits. More interestingly, we discovered a natural paradigm of social touch-like tactile stimulation being able to effectively normalize the impaired contagious pain of MS mice through enhancing the activity of the PVT→mPFC circuit. Collectively, our findings reveal a fundamental role for PVT→mPFC projection in empathic contagious pain, the dysfunction of which might pose the risk for inducing later deficits in empathic ability. These results provide useful insights into developing therapeutic strategies to treat brain disorders associated with the empathic impairments caused by childhood adverse experiences.



Disclosures: Z. Zhang: None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.27/K30

Topic: F.03. Stress and the Brain

Support: NIMH RO1 MH098348
NIMH T32 MH129174

Title: Violence Exposure, Psychosocial Stress, and Prefrontal Cortex Reactivity

Authors: *C. EICKSTEAD[1], E. DAVIS[1], A. M. GOODMAN[2], J. B. PURCELL[3], H. E. DARK[4], D. K. GREY[5], A. BOLARAM[5], T. R. OREM[6], M. WHEELOCK[1], S. MRUG[1], D. C. KNIGHT[7];
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Abstract: Abstract Adolescent violence exposure (VE) is a chronic stressor that has detrimental effects on emotional well-being, leading to higher rates of mental illness in adulthood. Adolescence is a period in life during which the brain, specifically the prefrontal cortex (PFC), undergoes extensive maturation. Chronic stressors, such as VE, experienced during adolescence may affect the development of the PFC. Thus, PFC activity may underlie the effects of adolescent VE on emotional processes. The present study examined the interrelationships between adolescent VE, stress-elicited young adult brain activity, and depression in young adults. Participants (n = 301; mean age = 20.03 ± 1.51 years), who were previously assessed for adolescent VE, completed the Major Depression Subscale of the Diagnostic Interview Schedule for Children. Participants then completed the Montreal Imaging Stress Task (MIST) during functional magnetic resonance imaging (fMRI). Pearson's correlation indicated that greater adolescent VE was linked to greater depression symptoms in young adulthood ($r = 0.12$, $p < 0.05$). Additionally, stress reactivity varied with VE. Specifically, greater VE was linked to lower stress ratings during the MIST ($r = -0.26$, $p < 0.01$). Further, linear mixed effects analyses of fMRI data revealed a three-way interaction between MIST condition (Stress vs. Control), VE, and depression symptoms. Specifically, stress-elicited ventrolateral (1323 mm^3) and dorsolateral (921 mm^3) PFC activity varied with VE and depression symptoms, with greater stress-elicited ventrolateral and dorsolateral PFC activity in those exposed to high levels of VE who reported high levels of depression than those exposed to high levels of VE who reported low levels of depression ($p < 0.05_{FWEcorrected}$). Additionally, participants with low VE who reported low levels of depression showed more stress-elicited ventrolateral and dorsolateral PFC activity than participants with low VE who reported high levels of depression. These findings suggest that depression modulates the link between adolescent VE and stress-elicited PFC activity. These results suggest that PFC function may underlie the relationship between adolescent VE and stress reactivity, but this relationship is further impacted by depression symptoms. The present findings provide insight into the neural substrates that underlie the interrelationship between adolescent violence exposure and stress reactivity, which may have important implications for future mental health.

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Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.28/K31

Topic: F.03. Stress and the Brain

Title: Effect of low-frequency Galvanic Vestibular Stimulation on Cardiac-Physiological and Psychometric Anxiety Parameters in Young Adults

Authors: *A. C. PLIEGO[1,2], E. ABARCA CASTRO[3], C. LEÓN CEDILLO[4], S. LIZARAZU[3]; [1]Facultad de Medicina UAEMEX, Toluca, Mexico; [2]Universidad Autónoma del Estado de México, Toluca, Mexico; [3]Univ. Autónoma Metropolitana - Lerma, Lerma, Mexico; [4]Univ. Autónoma del Estado de México, Toluca, Mexico

Abstract: Anxiety is a combination of mental and physiological manifestations that cannot be attributed to the presence of real danger. The functional value of anxiety resides in anticipating a life-threatening situation; it is an adaptative biological mechanism of self-protection against potential threats. If signs of anxiety surpass the expected intensity, frequency, or duration and appear without a threatening stimulus, pathological manifestations occur on a functional and emotional level. The vestibular system takes part in postural, oculomotor, cardiovascular, and cognitive functions. Interestingly, several mental disorders have been associated with vestibular dysfunction. Galvanic vestibular stimulation (GVS) is a noninvasive electrical stimulation method that applies an electrical current over the mastoid process to activate the end organs of the vestibular system. Previous research has probed the reduction of anxiety levels with low-frequency periodical movement. As GVS has been considered as an analog to mechanical stimulation, recent studies have explored if GVS provokes an equivalent effect on anxiety levels. However, we found no studies describing the impact of GVS on an anxiety level scale in combination with physiological parameters. Our study aims to make an integral description of the effect of low-frequency GVS on anxiety levels evaluated with a Visual Analog Scale for Anxiety (VASA) and with heart rate variability (HRV) parameters. Forty young subjects (20 M, 20 F) that obtained more than 30 points in the State-Trait Anxiety Inventory (STAI) were randomly divided into two groups, STIM and SHAM. In the STIM group, bilateral bipolar 0.2 Hz 1 mA GVS was applied for 15 minutes on five consecutive days while lying supine. In the SHAM group, the same procedure was performed but no GVS was administered. Electrocardiography (ECG) recording was acquired on days one and five for each subject. Subjects completed a VASA before and after each session. RR intervals were extracted, time-domain and frequency-domain HRV parameters were calculated using Kubious HRV Scientific software. When comparing HRV parameters before and after stimulation, we found no statistical differences between STIM and SHAM in mean RR interval, HR, SDNN, RMSSD, NN50, pNN50, PNS Index, SNS Index; nor in VLF, LF, and HF peak and power values. In contrast, the mean VASA of the STIM group showed a more significant decrease than the SHAM group when comparing before and after values. Our results indicates that GVS provokes a short-term reduction of anxiety symptomatology without altering cardiovascular autonomic variables (sympathetic/parasympathetic balance) of HRV.

Disclosures: A.C. Pliego: None. **E. Abarca castro:** None. **C. León Cedillo:** None. **S. Lizarazu:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.29/K32

Topic: F.03. Stress and the Brain

Title: Early-life stress and adult anxiety influence memory system bias in humans

Authors: *T. M. GADBERRY[1,2], G. M. ALEXANDER[3], M. G. PACKARD[3];
[1]Psychological and Brain Sci., Texas A&M Univ., Houston, TX; [2]Texas A&M University, College Station, TX; [3]Texas A&M Univ., College Station, TX

Abstract: In mammals, the hippocampal-dependent cognitive memory system supports spatial learning and allocentric associations, while the dorsolateral striatum (DLS) governs the S-R habit memory system and egocentric behaviors. Extensive evidence suggests that early-life stress (ELS) alters these memory systems' structural and functional development. Chronic ELS in humans is also linked with a predisposition to psychopathologies characterized, in part, by maladaptive habitual behaviors, such as OCD, PTSD, and SUD. Yet, few studies have explored how ELS affects memory systems in adulthood, particularly through the lens of a dual-solution navigation paradigm. This study assessed the performance and navigation strategy biases of 209 undergraduates (124 females) in the Virtual Boundary Landmark Task (VBLT; adapted from Doeller et al., 2008). The VBLT emulates principles of the Morris water maze used with rodents and concurrently tests allocentric and egocentric navigation linked to hippocampal and dorsal striatal functions, respectively. Participants learned to replace four items in a 3D arena, initially unaware that two items remained stationary (boundary-tied) while two periodically moved in relation to a single intramaze cue (landmark-tied). We evaluated strategy preference and memory system bias using a probe trial immediately following the intramaze landmark's initial relocation. Participants' chosen locations revealed their relative reliance on allocentric associations from the boundary’s fixed distal elements versus egocentric proximity to the landmark. We then administered the Creature of Habit Scale, State-Trait Anxiety Inventories, and Childhood Trauma Questionnaire to measure ELS. Participants successfully learned to replace both item types in the VBLT, with females demonstrating similar learning rates to males but with lower overall accuracy. Although state and trait anxiety levels were higher in females, these did not account for the observed differences in accuracy. In line with acute stress models, state anxiety reduced the boundary’s influence on probe trial choice, favoring landmark-based strategies, and was exacerbated with greater ELS. Our results crucially show that among individuals with moderate to severe ELS, higher trait anxiety and habitual tendencies in adulthood are associated with greater reliance on the proximal landmark in the probe trial, independent of sex. This bias towards habitual memory system use during navigation suggests ELS can alter the relative use of memory systems in adulthood and may contribute to the risk of psychopathologies.

Disclosures: T.M. Gadberry: None. **G.M. Alexander:** None. **M.G. Packard:** None.

Poster

PSTR471: Early-Life Stress: Effects on Anxiety, Social Function, and Depression

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR471.30/K33

Topic: F.03. Stress and the Brain

Support: Drexel University Medical Cannabis Research Center, Grant Number 480159-6326

Title: Trauma exposure moderates the strain-dependent efficacy of cannabis for the treatment of anxiety symptoms

Authors: T. HANBACK[1], R. STERLING[2], E. J. VAN BOCKSTAELE[2], *J. A. ROSS[3,2]; [2]Dept. of Pharmacol. & Physiol., [1]Drexel University, Col. of Med., Philadelphia, PA; [3]Global Neurosciences Inst., Pennington, NJ, NJ

Abstract: While significant evidence supports the therapeutic potential of targeting the endogenous cannabinoid system (ECS) with medicinal marijuana in adult patients with stress disorders, significant gaps in knowledge have hindered advancement. This investigation tested the hypothesis that medicinal marijuana is effective in treating symptoms of stress-related anxiety disorders in a stress exposure-, strain-, and dose-dependent manner. A survey-based, observational cohort study design was utilized and included 53 adults with valid prescriptions for medicinal marijuana to treat anxiety. Over two weeks, participants completed the State-Trait Anxiety Inventory (STAI) before and after medicinal marijuana consumption to quantify its therapeutic effect on clinical symptoms of anxiety. The Adverse Childhood Experiences (ACEs), and the Life Stress Checklist surveys were used to determine early life and late life trauma exposure, respectively. Group assignment included: No Trauma (≥3 ACEs), Early Trauma (4≤ ACEs), Late Trauma, or both. Repeated measures Analysis of Variance (ANOVA) found a statistically significant difference between each participant's 2-week average STAI score before and after medicinal marijuana consumption that was moderated by Trauma Exposure ($F(2,320)=88.13$; $p<0.0001$****) and Cannabis Strain ($F(2,320)=3.17$; $p=0.04$). Additionally, there was a significant interaction between Trauma Exposure and Cannabis Strain ($F(4,320)=8.2$; $p<0.0001$****), regardless of a participant's change in score. A clinically significant improvement in score was operationalized as having a reduction in STAI score by 10-points or more (per MCID standard). Within the No Trauma group, there were 28 occurrences of this type when treated with an Indica strain, 12 occurrences when treated with sativa strain and 14 occurrences in those treated with a hybrid strain. These results translate to Indica strains as a potential optimal treatment strategy for patients without a history of trauma. In a similar fashion, individuals with a history of early and late trauma would ideally be treated with an Indica strain as well. Finally, a sativa strain is most likely to effectively treat a patient with late Trauma, or trauma in their adult life (Fischer's Exact Test $p=0.0019$**).

Disclosures: T. Hanback: None. **R. Sterling:** None. **E.J. Van Bockstaele:** None. **J.A. Ross:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.01/K34

Topic: F.03. Stress and the Brain

Support: NIH Grant AA025677
NIH Grant DA011289

Title: Sex differences in neural circuit organization and motivated behavioral roles of cholecystokinin (CCK) neurons in the extended amygdala

Authors: H. SARDAR[1], ***Y. MA**[1], J. A. KAUER[2], W. J. GIARDINO[1];
[1]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA

Abstract: The bed nucleus of the stria terminalis (BNST) in the extended amygdala is a brain region that acts as a hub regulating internal states, emotions, and motivated behaviors. The BNST comprises diverse peptidergic neuronal populations, projecting locally and distally to regions modulating stress, reward, and social behavior. Previous work suggested that cholecystokinin (CCK)-expressing BNST subpopulations drive reward-related behaviors. The BNST is also characterized by sexual dimorphism; for example, over 800 genes, including CCK receptor genes, exhibit sexually divergent expression in posterior BNST neurons. However, whether the BNST-CCK neurons display sexual dimorphism in circuit organization and behavioral function is not fully understood.

Here we utilized anatomical, physiological, and behavioral methods to investigate sex differences in BNST-CCK neurons. CCK-expressing neurons were enriched in the posterior BNST of males compared to females, and posterior BNST-CCK neurons in male mice were preferentially activated by odorant stimuli from opposite-sex mice based on cFos analyses. Using anterograde viral tracing techniques, we identified anatomical evidence for a more prominent synaptic projection from BNST-CCK neurons to the medial amygdala (MeA) in males, perhaps suggesting a sex-specific role for BNST-CCK neurons in regulating motivated and social behaviors.

Recent advancements in GRAB sensors offer promising opportunities to unravel the role of endogenous neuropeptide release in intact tissue and in freely moving animals. To explore whether BNST-CCK neurons modulate social behaviors via CCK release, we virally delivered GRAB-CCK sensors to the BNST to detect neuropeptide release *ex vivo* and *in vivo*. We validated the GRAB sensor in brain slices by applying exogenous CCK and observing an elevated fluorescent signal. During *in vivo* fiber photometry recordings, GRAB-CCK signals increased when the animal was presented with a novel conspecific, suggesting that BNST CCK release corresponds to social reward. Taken together, these results uncover sex differences in

BNST-CCK neurons, suggesting CCK neuropeptide receptor signaling as a critical modulator of sex-specific behaviors.

Disclosures: H. Sardar: None. **Y. Ma:** None. **J.A. Kauer:** None. **W.J. Giardino:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.02/L1

Topic: F.03. Stress and the Brain

Support: STI2030-Major Projects (2021ZD0203000 (2021ZD0203001))

Title: Neural mechanism underlying depressive-like state associated with social status loss

Authors: *Z. FAN[1], J. CHANG[1], Y. LIANG[2], H. ZHU[3], C. ZHANG[4], D. ZHENG[1], J. WANG[1], Y. XU[1], H. HU[1];
[1]Zhejiang Univ. Sch. of Med., Hangzhou, China; [2]UC Berkeley, Albany, CA, ; [3]Inst. of Neurosci., Shanghai City, ; [4]Zhejiang Univ., Hangzhou.

Abstract: Downward social mobility is a well-known mental risk factor for depression, but its neural mechanism remains elusive. Here, by forcing mice to lose against their subordinates in a non-violent social contest, we lower their social ranks stably and induce depressive-like behaviors. These rank-decline-associated depressive-like behaviors can be reversed by regaining social status. *In vivo* fiber photometry and single-unit electrophysiological recording show that forced loss, but not natural loss, generates negative reward prediction error (RPE). Through the lateral hypothalamus, the RPE strongly activates the brain's anti-reward center, the lateral habenula (LHb). LHb activation inhibits the medial prefrontal cortex (mPFC) that controls social competitiveness and reinforces retreats in contests. These results reveal the core neural mechanisms mutually promoting social status loss and depressive behaviors. The intertwined neuronal signaling controlling mPFC and LHb activities provides a mechanistic foundation for the crosstalk between social mobility and psychological disorder, unveiling a promising target for intervention.

Disclosures: Z. Fan: None. **J. Chang:** None. **Y. Liang:** None. **H. Zhu:** None. **C. zhang:** None. **D. Zheng:** None. **J. Wang:** None. **Y. Xu:** None. **H. Hu:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.03/L2

Topic: F.03. Stress and the Brain

Support: NIH Grant EY019049
NIH Grant MH116990
NIH Grant R01DC008983
NIH Grant RF1MH114112

Title: Excitation-inhibition imbalance in medial preoptic area circuits underlies stress-induced depressive-like states

Authors: *C. TAO;
USC, Los Angeles, CA

Abstract: Maintaining the balance between neuronal excitation (E) and inhibition (I) is essential for normal brain function, with imbalances implicated in neuropsychiatric conditions such as major depressive disorder (MDD). The link between diverse etiological factors of MDD and E/I dysregulation at circuit levels remains not well-understood. In this study, we found that both physical and social stress are associated with an increase of E/I ratio in the medial preoptic area (MPOA), but through modulations of two distinct neuronal populations. Chronic restraint stress results in elevated activity in glutamatergic neurons without significant changes in GABAergic neurons, and inhibiting the glutamatergic neurons mitigates the stress-induced depressive-like behaviors. MPOA's input from the periventricular nucleus of the hypothalamus (PVN) contributes primarily to the induction but not expression phase of the depressive-like behaviors. MPOA glutamatergic projections to the ventral tegmental area (VTA) and periaqueductal gray (PAG) suppress midbrain dopaminergic and serotonergic activity, respectively, leading to expression of divergent depressive-like symptoms. In contrast, chronic social defeat stress results in reduced GABAergic activity without significant changes in glutamatergic activity, and activating the GABAergic neurons alleviates depressive-like behaviors. Thus, an imbalance of E/I ratio in MPOA circuits, skewed towards excitation, may be a common factor in stress-induced depressive-like states.

Disclosures: C. Tao: None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.04/L3

Topic: F.03. Stress and the Brain

Support: NIH Grant R01MH122844-02

Title: Chronic stress alters dynamic activity of lateral habenula neurons and facilitates behavioral engagement during flexible decision making

Authors: *Z. FISHER, R. M. SCHMID, H. R. WRIGHT, G. GIANNOTTI, R. J. MCLAUGHLIN;
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Abstract: The ability to integrate feedback and flexibly adjust behavior under shifting environmental demands is required to optimize decision-making strategies. Clinical and preclinical data indicate that individuals with stress-related disorders and rodents exposed to chronic stress exhibit impaired behavioral flexibility, though the underlying neural mechanisms remain elusive. The lateral habenula (LHb) has emerged as a key brain region contributing to the effects of stress and cognitive performance, which it accomplishes via indirect projections that effectively inhibit the activity of downstream monoaminergic nuclei that orchestrate decision-making strategies. However, the extent to which the LHb is recruited to fine-tune decision-making strategies, as well as the impacts of chronic stress on LHb recruitment during task performance, remain largely unknown. To this end, we used a three-week model of chronic unpredictable stress (CUS) consisting of 2-3 randomized stressors per day and *in vivo* fiber photometry measurements of a genetically encoded Ca^{2+} indicator (GCaMP6) in LHb neurons during an attentional set-shifting task in adult male and female Sprague Dawley rats (n=5-9/sex/group) to test our hypothesis that chronic stress alters activity of LHb neurons specifically after incorrect response trials, which compromises feedback integration to significantly impair behavioral flexibility. Contrary to our hypothesis, our results indicate that CUS exposure did not significantly impair behavioral flexibility. Instead, CUS-exposed rats unexpectedly made fewer omissions and exhibited shorter response latencies compared to control rats, which may be indicative of enhanced vigilance and/or task engagement. Interestingly, sex differences in the activity of LHb neurons were observed, with female rats exhibiting more LHb activity than males prior to making a choice, and male rats exhibiting more LHb activity than females after making a choice. Sex differences were also observed in the effects of CUS on LHb activity. Specifically, CUS females exhibited a transient suppression of LHb activity prior to making a correct response compared to control females, whereas CUS males showed the opposite pattern by exhibiting attenuated suppression of LHb activity compared to control males. Sex-dependent trends in LHb activity were also observed during the post-response period, with males exhibiting greater LHb activity than females - however, this effect was completely absent in CUS-exposed rats. Overall, our data suggest a complex relationship between chronic stress and behavioral flexibility and reveal novel sex-specific adaptations in LHb recruitment.

Disclosures: Z. Fisher: None. **R.M. Schmid:** None. **H.R. Wright:** None. **G. Giannotti:** None. **R.J. McLaughlin:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.05/L4

Topic: F.03. Stress and the Brain

Support: 5R25NS130966-02

Title: Exploring the Impact of Social Touch Perception and Isolation on Brain Networks of Stress Vulnerability

Authors: *O. CHRISTIAN[1], M. MATKOVICH[2], M. SCHAFFLER[3], M. JOHNSON[4], S. L. FULTON[5], I. ABDUS-SABOOR[6], R. HULTMAN[7];
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Abstract: Stress is universally experienced in nature and challenges an organism's ability to maintain homeostasis. In humans, this can contribute to the onset of psychiatric disorders. In species that behave socially, tactile social interaction (social touch) has been shown to be a natural reward. In previous studies, mice isolated from cage mates displayed increased anxiety and depressive behavior, impaired prefrontal cortex development and deficits in spatial memory. The experience of isolation in such species is a major stressor that negatively impacts quality of life. Current literature suggests that stress experienced during social isolation is driven by a lack of social touch. The impact of social touch on the brain and behavior is also explored in a mouse model where ablation of Mrgprb4-lineage (social touch) neurons blunts the response to normally rewarding stimuli. We hypothesize that reducing social touch stimulation through genetic manipulation and isolation, results in altered behavior and brain networks. Behavioral and neurophysiological data were collected from ablated mice (n=7) and wild-type controls (n=10), as well as isolated mice (n=9) and group-housed controls (n=10) at baseline and after exposure to stress. Mrgprb4-lineage neuron ablated mice displayed a behavioral phenotype of less grooming time in the sucrose splash test ($p < 0.05$) and increased immobility in the forced swim test ($p < 0.05$) following stress when compared to wild-type controls. Isolated mice displayed an increased interaction time during the direct juvenile interaction assay (males: $p < 0.05$, females: $p < 0.01$) when compared to group-housed controls. Local field potential (LFP) data were collected from mice in each of the ablated, isolated, or control conditions. LFPs were analyzed by quantifying previously identified stress vulnerability networks, also known as "electome factors", or electrical functional connectomes/networks. A stress vulnerability network was able to differentiate between ablated and wild-type mice after an acute sucrose splash (average of individual animals' AUCs = 0.7691, σ=0.1756; AUC of both averaged groups = 0.9519). This stress vulnerability signature in ablated mice is significantly higher following sucrose splash ($p < 0.0001$) when compared to wild-type controls. Blockage of the perception of social touch results in differences in behavior and altered stress vulnerability network activity. These data suggest brain-network level mechanisms underlying a pro-resilience effect of social touch in the face of stress. Further studies examine if social isolation evokes the same electrical network phenotypes as the genetic manipulation.

Disclosures: O. Christian: None. **M. Matkovich:** None. **M. Schaffler:** None. **M. Johnson:** None. **S.L. Fulton:** None. **I. Abdus-Saboor:** None. **R. Hultman:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.06/L5

Topic: F.03. Stress and the Brain

Support: R21 DA059966
R01 DA056534

Title: Early life resource scarcity and motivation for natural rewards in adolescent rats

Authors: *E. P. HARRIS[1], K. MESAPE[2], E. ANDREWS[2], D. A. BANGASSER[2];
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Abstract: Resource scarcity in early life is associated with increased risk for developing disorders characterized by altered motivated behavior, including major depressive disorder and substance use disorder. We have previously used the limited bedding and nesting (LBN) model in rats to demonstrate that early resource scarcity has a sex-specific effect on reward-related behaviors in adults, such as self-administration of sucrose and social rewards, morphine self-administration, and delay discounting. Specifically, LBN increased motivation for social and sucrose rewards in adult males, whereas in adult females, LBN decreased motivation for sucrose rewards with no effect on social reward motivation. During adolescence, substantial remodeling and maturation occurs in brain areas involved in motivation and reward signaling such as the prefrontal cortex and nucleus accumbens. However, the effects of early resource scarcity on reward-related behaviors in adolescence are understudied. Thus, we aimed to determine the impact of early resource scarcity on motivation for natural rewards in adolescents. Male and female Long Evans rats were reared in either an LBN environment, with limited nesting materials and no enrichment, from postnatal day 2-9 or the control environment with ample nesting materials and enrichment. Beginning at postnatal day 38, two separate cohorts of adolescent rats were trained to press a lever to earn a reward: either sucrose pellets or access to a novel same-sex, same-age conspecific. Adolescents underwent an operant conditioning task at a fixed-ratio 1 (FR1) schedule for 4 days, then at an increasing ratio of FR2, FR4, and FR8 for 2 days each. On postnatal day 50, the rats were tested on a progressive ratio (PR) trial, where the lever responses required for each reward increases exponentially until the rat fails to reach the requirement. Studies are ongoing but preliminary data suggest that, unlike in adulthood, LBN may not affect motivation for sucrose in adolescence. This suggests that maturation of reward circuits during the adolescent period may modulate the effects of early life scarcity and highlights the importance of studying the developmental trajectory of early stress on reward-related behavior.

Disclosures: E.P. Harris: None. **K. Mesape:** None. **E. Andrews:** None. **D.A. Bangasser:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.07/L6

Topic: F.03. Stress and the Brain

Support: NSF GRANT IOS 2137023
NIH/NIMH GRANT R01MH132018-02

Title: Acute stress perturbs synaptic mechanisms underlying learning-induced plasticity

Authors: *A. VATS[1], O. M. OGUNDELE[2];
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Abstract: Stress disrupts brain homeostasis by altering neural activity, and synaptic substrates that underlie cognitive and adaptive processes. Acute stress paradigms have been associated with perturbations in the pathways linked with synaptic plasticity and long-term potentiation in the cognitive centers. Previous studies have shown sex-linked differences in the molecular signal profile and neural circuits associated with adaptive stress response. The current study investigates novel mechanisms through which acute physical stress alters learning-induced synaptic plasticity. Here, we examined stress sensitivity in reward-oriented spatial learning, and alterations of substrates implicated in stress signaling or synaptic plasticity. **Methods:** Adult C57BL/6J mice were subjected to daily physical restrain stress (2h), followed by a washout period (30 m), then a T maze task driven by reward contexts. At the end of a 6-day period, animals were assessed for stress-linked behavior in Elevated Plus Maze (EPM) and Open Field tests. Ultimately, prefrontal cortical, hippocampal, and paraventricular hypothalamic brain samples were obtained by microdissection, and processed for detection of proteins (immunoblot) and determination of gene expression patterns (PCR). **Results:** After acute restraint stress, female mice showed a decline in task learning propensity compared with males exposed to similar conditions. In a reward-oriented spatial T maze task, stressed female mice have lower learning outcomes when compared with control. Conversely, stressed male mice show robust learning outcomes and were comparable with the controls. In support of this result, stressed male mice required less time to complete the trials of a T maze task in comparison with the control or stressed female groups. Analysis of anxiogenic behavioral outcomes - in EPM tests - at the end of learning sessions revealed aberrant frequency of open-closed arm transitions for stressed female mice. Protein location outcomes showed perturbations in translocation pattern of synaptic and stress signaling substrates, especially in female mice. These results suggest stress-linked changed in learning induced plasticity may be sex-linked. **Conclusions:** Taken together, our results show that physical stress decreased daily spatial learning outcomes in female mice, compared to males.

Disclosures: A. Vats: None. **O.M. Ogundele:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.08/L7

Topic: F.03. Stress and the Brain

Support: R01MH121829
R01MH121829-04S1

Title: Effects of CRISPR-based knock down of oxytocin receptors in bed nucleus of the stria terminalis and nucleus accumbens on social approach and vigilance behaviors

Authors: *V. I. CEA SALAZAR[1], A. J. BOENDER[2], L. J. YOUNG[3], B. C. TRAINOR[1]; [1]Psychology, Univ. of California, Davis, Davis, CA; [2]Silvio O. Conte Ctr. for Oxytocin and Social Cognition, Emory Univ., Atlanta, GA; [3]Ctr. for Translational Social Neurosci., Emory Univ., Decatur, GA

Abstract: Mood disorders, like anxiety and depression are prevalent in the US and current therapeutic approaches are not effective for many individuals. There is a strong need for new treatment approaches, and identifying neurobiological mechanisms behind these disorders can play an important role in this effort. Social behavior networks in the brain have been identified using techniques ranging from pharmacology to optogenetic manipulations in rodent models. The Bed Nucleus of the Stria Terminalis (BNST) is implicated as a key region driving social avoidance and vigilance behaviors. In contrast, the Nucleus Accumbens (NAc) is more involved in social approach and pair-bond formation. Importantly, oxytocin receptors acting in the NAc and BNST have been found to exert profoundly different effects on social approach and vigilance. Previous work relied on pharmacological manipulations which target pre- and post-synaptic receptors. Here, we use a CRISPR-based gene editing approach to knock down oxytocin to determine the contribution of post-synaptic oxytocin receptors on behaviors. Using the California mouse social defeat model, we take advantage of the stronger social avoidance phenotype in females versus males. Preliminary data from BNST experiments suggest that post-synaptic receptors play a key role in mediating the effects of oxytocin on behavior. Females that received a control guide RNA in the BNST showed significantly reduced social interaction following social defeat stress compared to *Oxtr* knockdown mice that sustained higher levels of social interaction after stress ($p=0.007$, $df=12$). In the post-stress "Acclimation" phase knockdown mice also had similar levels of interest with the empty wire cage compared to when the Target mouse was placed during the "Interaction" phase. Control mice however showed interest and interacted more with the empty cage during "Acclimation" and significantly reduced their average interaction time by half once a Target mouse was placed ($p=0.005$, $df=5$). These data suggest that post-synaptic oxytocin receptors promote stress-induced social avoidance in females. Ongoing studies are testing whether this effect generalizes to male mice. Future studies could then focus on identifying the cell types underlying these effects.

Disclosures: V.I. Cea Salazar: None. **A.J. Boender:** None. **L.J. Young:** None. **B.C. Trainor:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.09/L8

Topic: F.03. Stress and the Brain

Support: NSF GRFP

Title: The neurobiology of social anxiety: examining the role of BNST to NAc projections

Authors: *A. J. GRAMMER;
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Abstract: The neurobiology of social anxiety: examining the role of BNST to NAc projections**J. Grammer, M. Zelikowsky**Prolonged social isolation has been shown to promote a host of deleterious effects on behavior including increased social anxiety; however, the neural mechanisms underlying this effect remains unknown. The nucleus accumbens (NAc) is integral to social behavior and has been implicated in social approach and avoidance. Alternatively, the dorsal bed nucleus of the stria terminalis (dBNST) is known for its role in mediating anxiety and social isolation stress. Thus, these regions represent prime candidates for the control of isolation-induced social anxiety. Importantly, the coordinated activity of these regions via their reciprocal, monosynaptic projections remains relatively unexplored on both an anatomical and functional level. Using fluorescent *in situ* hybridization (RNAscope) probing for the bi-directional neural activity marker EGR1, we found that isolation increases activity in the dBNST and decreases NAc activity. This suggests that an imbalance of activity in this pathway may underlie the effects of social isolation to impact social behavior. Next, using a chemogenetic loss-of-function approach, we found that the NAc is required for social approach in a three-chamber sociability assay. To comprehensively investigate social anxiety-like behavior in mice, we developed a new assay, Selective Access to Unrestricted Social Interaction (SAUSI), in which mice have the choice to pass through a small, one-way tunnel to freely interact with a conspecific mouse. Using in-depth observer scoring as well as automated machine-learning approaches, we found that social isolation stress increases social anxiety as indexed by social freezing and approach hesitancy, while altering complex social behaviors measured during free interaction. Collectively, these findings support the hypothesis that this pathway lies at the intersection between social behavior and anxiety. We are currently investigating the contribution of genetically defined dBNST to NAc projection cells in isolation-induced social anxiety-like behavior. Ultimately, our project defines a mouse model of social anxiety using a novel social choice assay that allows for motivated *and* free interaction, unveils isolation induced changes in neural activity in the dBNST and NAc, and explores a novel role for this circuit in isolation induced social anxiety-like behavior.

Disclosures: A.J. Grammer: None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.10/L9

Topic: F.03. Stress and the Brain

Title: Effects of sub-chronic corticosterone administration on amphetamine-conditioned place preference in C57BL/6J mice

Authors: Y. AVBOVBO[1], C. TEVES[2], M. E. CRONIN[3], ***A. BASU**[1];
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Abstract: High stress levels are correlated with increased drug use and the establishment of context-related drug acquisition patterns. Using conditioned place preference (CPP) as a model for drug-seeking behavior, many studies have observed that experimental administration of corticosterone (CORT) potentiates drug-induced reinstatement of CPP in rats and mice. However, few studies have observed the effects of CORT on acquisition of drug-seeking behavior in this paradigm, and none have previously investigated effects of CORT on CPP in female mice. This study used noninvasive administration of CORT to mimic HPA axis activation, and observed subsequent acquisition of amphetamine-seeking behavior in male and female C57BL6/J mice. We administered CORT (0.06 mg/ml or 0.11 mg/ml) sub-chronically (throughout the duration of testing) via the drinking water and subjected mice to a four-day protocol to induce CPP. Mice were place conditioned using 1.5 mg/kg of amphetamine (AMPH) injected subcutaneously as reinforcement. Male mice treated with the low dose of CORT showed attenuation of place conditioning. The high dose of CORT resulted in weight gain in males and the low dose of CORT resulted in weight loss in females. These results suggest a relationship between CORT levels and the emergence of drug-seeking behavior, and are consistent with previous reports of a complex relationship between CORT levels and body weight.

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Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.11/L10

Topic: F.03. Stress and the Brain

Support: NSF GRFP
RO1-MH115914

Title: Exploring the impact of early life adversity on dopamine dynamics in methamphetamine conditioned place preference

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Abstract: Experiencing early life adversity (ELA) increases the risk of substance use disorders (SUDs) and stress-induced relapse following abstinence. The use and abuse of methamphetamines (MA), is a major public health concern with profound psychiatric, medical, and psychosocial complications. Psychostimulants primarily exert their rewarding effects by increasing extracellular dopamine (DA) in the striatum, and the pursuit of reward and stress-induced reinstatement (a model of relapse) has been shown to be mediated by DA release as well as the corticotropin-releasing factor (CRF). Specifically, CRF microinjections into the nucleus accumbens (NAc) induce conditioned place preference (CPP) and amplify incentive salience of reward-related cues, a process thought to underlie stress-induced reinstatement (SIR).
Disruptions in the CRF system following ELA have been implicated in a host of stress- and reward-related behaviors, particularly in the central amygdala (CeA) and basolateral amygdala, which act as integrative hubs for stress and reward circuitry and innervate the NAc. Converging evidence has demonstrated that CRF projections to the NAc from the amygdala modulate reward related behavior and that these regions are functionally connected. Recent work has shown that excitation of CRF neurons in the CeA and the NAc amplifies incentive motivation to pursue cocaine-paired cues. Additionally, others have shown that animals exhibit a robust increase in DA release in the NAc core upon entry into a heroin-paired compartment.
Although evidence suggests that ELA disrupts both DA and CRF signaling within reward- and stress-related regions, the link between these two overlapping systems and how ELA disrupts signaling to promote drug abuse remains unclear. Critically, the contribution of CRF signaling and its modulation of DA release during CPP and SIR and how that activity may be impacted by ELA has yet to be elucidated.
Using an 8-day CPP paradigm, I have demonstrated that animals robustly display place preference for the MA paired compartment following 4 days of conditioning. My preliminary data also show that a higher percentage of ELA animals exhibit enhanced place preference to the drug-paired side following conditioning (defined as a CPP score above 300s). In my ongoing work, I will employ fiber photometry and genetically encoded sensors for both CRF and DA to measure the impact of ELA on CRF-mediated DA release in the NAc during MA-induced CPP and SIR. Together, these studies have the potential to significantly improve our understanding of the development of SUDs in at-risk populations and provide insight into the development of novel treatment strategies.

Disclosures: B.L. Williams: None. **K.G. Bath:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.12/L11

Topic: F.03. Stress and the Brain

Support: NIMH 1R21MH133212
NIMH F30MH134633
NIMH T32NS048004
NIGMS T32GM008042

Title: A Cell-Type Specific Circuit Mechanism Underlying the Antidepressant-like Effects of Transcranial Magnetic Stimulation

Authors: *A. QI[1], M. GONGWER[2], A. ENOS[3], C. KLUNE[4], A. Q. KASHAY[5], Y. YANG[6], A. LEUCHTER[7], H. LU[8], L. A. DENARDO[2], S. WILKE[1];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method for brain stimulation that is an emerging treatment for depression and other neuropsychiatric disorders. Clinical rTMS is proposed to exert therapeutic effects by driving neuroplastic changes in cortical networks. However, the underlying circuit changes are poorly understood, limiting the rational design of more precise and effective treatment protocols. Here, we present a novel preclinical model of rTMS, utilizing the first rodent coil capable of both highly focal (<2mm) and suprathreshold stimulation of a cortical subregion. By combining medial prefrontal cortex (mPFC) targeted clinical rTMS with chronic stress, fiber photometry and chemogenetics we reveal a cell-type specific mechanism by which rTMS may drive therapeutic effects in depression. We show that accelerated intermittent theta-burst stimulation (iTBS) over mPFC can reverse behavioral deficits associated with chronic stress. Using fiber photometry, we recorded neural dynamics from cortex-projecting intratelencephalic (IT) neurons, subcortical-projecting pyramidal tract (PT) neurons, and parvalbumin (PV) interneurons in mPFC during and after accelerated iTBS. Each mPFC cell type responded uniquely during iTBS. All cell types responded to individual iTBS trains with an acute increase in activity. However, across a 10-minute iTBS session, IT neurons exhibited increasing activity over time, while PT and PV neurons displayed a trend of decreased activity. One day later, iTBS-treated animals displayed enhanced IT neuron activation during effortful responses to an inescapable stressor and suppressed PV activity in response to an aversive stimulus. Chemogenetic suppression of IT neuron activity during accelerated iTBS was sufficient to block the antidepressant-like effects of stimulation. Together, these results reveal a critical role for cell-type specific plasticity in the therapeutic effects of rTMS.

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Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

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Program #/Poster #: PSTR472.13/L12

Topic: F.03. Stress and the Brain

Support: NIH Grant R01MH118237

Title: Repeated social stress increases risk assessment in adult male rats

Authors: C. STICKLING, *J. ROSENKRANZ;
Chicago Med. Sch., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Anxiety impacts more than a third of Americans at some time during their life. Stress is a major trigger for anxiety. But anxiety has multiple behavioral manifestations and we still do not fully understand what components are sensitive to stress. Rodents explore novel contexts, and their degree of exploration is highly sensitive to stress. During exploration, rodents engage in risk assessment behaviors, and this is believed to contribute to decision-making regarding the degree of exploration. However, it is not clear how stress impacts risk assessment, and if this is tied to effects of stress on exploration. Here we examined behavior in the Elevated Plus Maze (EPM) to track exploration and risk assessment in parallel, and to test if repeated stress jointly impacts exploration and risk assessment in adult male rats. We hypothesized that repeated stress will increase risk assessment behaviors and bias behaviors towards less risky exploration in the EPM. Risk assessment was measured with stretching, rearing, and over-edge looking behaviors. To further test the link between risk assessment and EPM exploration, we tested the effects of diazepam, an anxiolytic that reduces the impact of stress on EPM exploration, on the link between risk assessment and exploration. We found that repeated social defeat stress increased open arm stretching compared to control rats, and, similar to prior studies, stressed rats spent less time in the open arm. Furthermore, stress increased the likelihood of risk assessment stretch behaviors prior to entering an open arm, and decreased the likelihood that a rat would enter an open arm after risk assessment. Diazepam ameliorated the effects of repeated stress within the EPM for both risk assessment and exploratory behavior, further linking anxiety-like behaviors and risk assessment. These results provide insight into the effects of stress on risk assessment, and the link between anxiety, risk assessment and subsequent risky behaviors.

Disclosures: C. Stickling: None. **J. Rosenkranz:** 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.; Aptinyx Inc.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.14/L13

Topic: F.03. Stress and the Brain

Support: NIH P50 MH096889
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NIH RO1 MH132680

Title: The targets of GABAergic CRH-expressing projections from the basolateral amygdala

Authors: *Y. CHEN[1], M. T. BIRNIE[2], T. Z. BARAM[3];
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Abstract: Background: The basolateral amygdala (BLA) is a heterogenous nuclear complex and projects to brain regions involving in reward, fear, and stress responses. Projections connecting brain regions are typically composed of several cell types defined by their neurotransmitter and often by a co-expressed neuropeptide. We have reported a GABAergic projection from the BLA to the nucleus of accumbens (NAc) that expresses the neuropeptide corticotropin-releasing hormone (CRH) (Birnie et al., Nat Commun 2023), while the majority of the literature suggests that the BLA-NAc projection is glutamatergic. Specifically, this GABAergic CRH+ projection from the BLA to the NAc represses reward behavior. Neuropeptide CRH has well-established roles in stress, addiction, and reward via specific cellular actions within NAc and several other brain regions, providing impetus for the comprehensive characterization of BLA-CRH projection cells. Here, we map BLA-CRH projections in mouse brain and characterize their target cells in the NAc. Methods: The cellular identity of the BLA-CRH projection cells and their targets within mouse brain were investigated by employing transgenic mice, anterograde and retrograde viral-genetic tracing, coupled with optogenetics. Results: CRH cells in the BLA co-localized with GAD mRNA and protein, but not glutamatergic markers. Optogenetic stimulation of the BLA-CRH projections in the NAc yielded exclusively IPSCs. Anterograde tracing via injection of pAAV-FLEX-tdTomato into the BLA of Crh-IRES-Cre mice identified CRH expressing projections from the BLA to the NAc, bed nucleus of the stria terminalis (BNST), prefrontal cortex (PFC), and ventral hippocampus (vHip). The use of rAAV2-retro DIO-CAG-tdTomato injected into above projection targets ascertained distinct subgroups of CRH projection cells in the BLA with distinct neuroanatomical segregation within the BLA. Combined retrograde tracing and optogenetics, coupled with immunohistochemistry suggested that D1R-expressing spiny cells and interneurons including PV-ir and ChAT-ir cells in the NAc were innervated by BLA-CRH projections. Conclusions: GABAergic CRH expressing cells across the BLA are projection cells, targeting brain regions important for stress, reward, and cognition. These cells can be classified as distinct subgroups and each subset of cells sends axonal projection, contacting with its specific target cells.

Disclosures: Y. Chen: None. **M.T. Birnie:** None. **T.Z. Baram:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.15/L14

Topic: F.03. Stress and the Brain

Support: CIHR

Title: Hypothalamic CRH neurons sense potential danger

Authors: *T. FUZESI, T. CHOMIAK, M. ROJAS-CARVAJAL, K. SIMONE, L. A. MOLINA, D. G. ROSENEGGER, N. RASIAH, N. DAVIU, W. NICOLA, J. S. BAINS;
Univ. of Calgary, Calgary, AB, Canada

Abstract: The anticipation of threat activates a defensive state to recruit specific circuits that elicit appropriate defensive behaviors. Threats, or dangers, however, are not always predictable. This unpredictability means specific brain systems must also anticipate and prepare for potential danger. This means some brain systems must be engaged even if danger never materializes. Here we report that CRH neurons in the paraventricular nucleus of the hypothalamus (CRH^{PVN}) that react to stressful stimuli by launching the endocrine response to stress, also respond to environments that signal potential danger. Imaging cellular activity by single fiber photometry and miniature microscopy in freely behaving mice reveals a response to a novel context in individual CRH^{PVN} neurons. Repeated exposure to the same context reveals that the anticipatory response does not track behavioral habituation. The ability to anticipate potential danger and take precautionary measures is advantageous, but inappropriate danger perception may be indicative of emergent neuropsychiatric disorders.

Disclosures: T. Fuzesi: None. **T. Chomiak:** None. **M. Rojas-Carvajal:** None. **K. Simone:** None. **L.A. Molina:** None. **D.G. Rosenegger:** None. **N. Rasiah:** None. **N. Daviu:** None. **W. Nicola:** None. **J.S. Bains:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.16/L15

Topic: F.03. Stress and the Brain

Support: NSERC Discovery Grant
CIHR Foundation Grant
IZAAK WALTON KILLAM MEMORIAL SCHOLARSHIP
Cumming School of Medicine Graduate Scholarship

Title: Acute exercise buffers stress-induced metaplasticity in CRH^{PVN} neurons and mitigates stress-induced defensiveness

Authors: *M. ROJAS-CARVAJAL[1], T. FUZESI[1], D. V. BAIMOUKHAMETOVA[1], N. DAVIU[2], K. SIMONE[3], S. COOK[1], J. S. BAINS[4];
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Abstract: Stress imprints biochemical, molecular, and synaptic changes in the brain to promote adaptation. However, these changes can become maladaptive and foster neuropsychiatric diseases. Surprisingly, there is limited understanding on how these imprints can be reversed. In humans, exercise is used to cope with stress despite inducing physiological stress itself. Here we examined the effects of exercise on stress-induced short-term potentiation (STP) of glutamate synapses on corticotropin release hormone cells in the paraventricular nucleus of the hypothalamus (CRH^{PVN}). Exercise (treadmill) for one hour after foot shock (FS) increased CRH^{PVN} activity and circulating corticosterone (CORT). Next, we obtained electrophysiological recordings from CRH^{PVN} neurons in hypothalamic slices and evaluated the effects of exercise after FS on STP. Following FS, high frequency stimulation of glutamate synapses elicited STP. Exercise after FS blunted STP. Exercise after FS increased brain-derived neurotrophic factor (BDNF) in the PVN. And incubation of brain slices from FS mice with a TrkB agonist and CORT blunted STP. At a behavioral level, mice subjected to FS showed lower exploration of the light compartment in a Dark/Light box. Exercise after FS reversed this phenotype. Our findings demonstrate that exercise increases BDNF in PVN and decreases STP induced by stress This is accompanied by a decrease in stress-induced anxiety.

Disclosures: M. Rojas-Carvajal: None. **T. Fuzesi:** None. **D.V. Baimoukhametova:** None. **N. Daviu:** None. **K. Simone:** None. **S. Cook:** None. **J.S. Bains:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.17/L16

Topic: F.03. Stress and the Brain

Support: NIH R01MH125898

Title: A Nucleus Accumbens-to-Dorsal Raphe Pathway Mediates Exercise-Induced Stress Resistance in Female Rats

Authors: *S. MELLERT[1], J. WESTERMAN[2], J. AMAT[3], M. K. TANNER[2], A. HOHORST[1], S. OBERTO[2], B. CANIELS[4], C. SANCHEZ[2], M. V. BARATTA[3], B. N. GREENWOOD[2];
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Abstract: Following a traumatic event, women are twice as likely as are men to develop a stress-related disorder, such as PTSD. Therefore, it is critical to identify processes that foster resistance against future adversity in females. Exercise is a potent stress resistance factor that reduces the incidence and severity of stress-related disorders. Indeed, preclinical models demonstrate that voluntary wheel running (VWR) prevents the typical depressive- and anxiety-like outcomes of inescapable stress (IS) in rats. Importantly, we have observed that female rats are more responsive than are males to the effects of exercise, attaining stress resistance after only 3 weeks of VWR compared to the 6 weeks of VWR required in males. In sedentary rats, IS potently activates serotonergic (5HT) neurons in the dorsal raphe nucleus (DRN), which is necessary and sufficient for behavioral outcomes such as social avoidance and exaggerated fear. Six weeks of VWR in males confers stress resistance by constraining the DRN 5HT response to IS. However, it remains unclear whether VWR similarly attenuates the DRN 5HT response to IS in females at an accelerated pace and the underlying mechanism of constraint. This study sought to determine if 3 weeks of VWR constrains the DRN 5HT response to IS in female rats. Additionally, we tested the necessity of a direct inhibitory pathway from the nucleus accumbens (NAc) to the DRN for exercise induced behavioral resistance. Adult, female Sprague-Dawley rats were single-housed and assigned to either voluntary exercise or locked wheel conditions for 3 weeks. Microdialysis revealed a significant attenuation of IS-induced 5HT efflux in the DRN in the VWR group compared to locked controls. This finding demonstrates that VWR constrains the DRN 5HT response to stress in females, providing, for the first time, a neurochemical basis for the previously observed rapid stress resistance produced by VWR in females. Furthermore, chemogenetic inactivation of the NAc-DRN pathway during IS restored stress-induced exaggerated fear in the VWR group, suggesting that NAc-DRN pathway activity during stress is necessary for the rapid stress-buffering effects of VWR in females. These data suggest that the NAc-DRN circuit is a novel stress resistance pathway, and the first identified in females.

Disclosures: S. Mellert: None. **J. Westerman:** None. **J. Amat:** None. **M.K. Tanner:** None. **A. Hohorst:** None. **S. Oberto:** None. **B. Caniels:** None. **C. Sanchez:** None. **M.V. Baratta:** None. **B.N. Greenwood:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.18/L17

Topic: F.03. Stress and the Brain

Support: Iowa Osteopathic Education and Research Foundation

Title: Estrogen-mediated resilience against stress-induced persistent physical inactivity

Authors: *M. MOHAMED[1], V. MATHIS[2], T. J. BUHR[3], C. REED[4], K. TEFFT[5], P. J. CLARK[4], S. CLAYTON[5], L.-L. YUAN[6];
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Abstract: Sedentary lifestyles are considered a leading cause of chronic and metabolic diseases affecting individuals globally. Among the many risk factors associated with physical inactivity, psychological stress emerges as a primary contributor. Thus, we investigated the impact of acute stress on physical activity using rodents and the voluntary wheel running (VWR) exercise model. Male and female rats were subjected to 100 tail shocks before VWR access was provided. Our findings revealed a sustained reduction in daily VWR distance among shocked male rats for weeks post-stress, extending beyond the duration of anxiety and depression-like behaviors. Conversely, shocked female rats did not exhibit sustained VWR reduction following the same stressor, indicating intriguing sex differences and suggesting a potential protective role of estrogen against stress-induced physical inactivity. Mechanistically, multiple factors such as exercise motivation or capacity may contribute to reduced VWR distances. While research has shown acute stress reduces exercise capacity in male rats via treadmill running, this area remains underexplored in females. Considering estrogen's known impact on female physical activity, it may underpin sex differences in exercise capacity, warranting investigation via treadmill running. Our ongoing work seeks to validate the hypothesis that estrogen acts against stress-induced declines in exercise capacity, fostering resilience in female rats. Understanding stress impact on physical activity capacity and estrogen's protective effects will inform strategies to alleviate sedentary lifestyles and mitigate stress's adverse effects on physical activity engagement.

Disclosures: M. Mohamed: None. **V. Mathis:** None. **T.J. Buhr:** None. **C. Reed:** None. **K. Tefft:** None. **P.J. Clark:** None. **S. Clayton:** None. **L. Yuan:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.19/L18

Topic: F.03. Stress and the Brain

Support: NIH R01 MH125898

Title: High estrogen during acquisition of wheel running promotes dopamine in the dorsolateral striatum and primes future physical activity

Authors: *K. KORTH[1], M. K. TANNER[1], A. A. HOHORST[2], J. WESTERMAN[1], E. B. OLESON[1], B. N. GREENWOOD[1];

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Abstract: Regular physical activity can prevent and reduce symptoms of stress-related mental health disorders, which occur at higher incidence in women than men. In rats, females display greater responsiveness to the stress-protective benefits of exercise compared to males. Thus, understanding factors that motivate physical activity in females is of particular importance. We have observed that females prefer to use habit circuitry involving the dorsolateral striatum (DLS) to govern voluntary wheel running, whereas males prefer to use goal-directed circuitry involving the dorsomedial striatum (DMS). Moreover, we found that dopamine (DA) release in the DLS is potentiated during phases of the rat estrous cycle characterized by high levels of estradiol (E2). Here, we tested the hypothesis that initiating voluntary wheel running (VWR) during high E2, either caused by natural fluctuations or exogenous administration, would facilitate development of habitual running in adult, female, Long Evans rats. Cycling female rats were granted initial access to novel VWR during the high E2 phase of their reproductive cycle, proestrus (PRO), or the low E2 phases metestrus and diestrus (MET/DI). Rats lacking ovaries (OVX) received either vehicle (VEH) or E2 injections 4 h prior to novel VWR at a dose replicating PRO E2 levels. Following 3-weeks of VWR, fast-scan cyclic voltammetry with carbon fiber microelectrodes placed in the DLS was performed to examine effects of estrous cycle or E2 on DA release. We observed that rats beginning VWR during PRO displayed greater average running distances and electrically-evoked DA release in the DLS compared to rats beginning VWR during MET/DI. E2 administration, relative to VEH, also increased VWR during the first week of VWR, and increased DA release in the DLS. These data provide support for the hypothesis that high E2 during the acquisition of VWR facilitates habitual VWR through a mechanism involving DLS DA. These results could inform novel strategies to increase exercise participation and adherence in women.

Disclosures: K. Korth: None. **M.K. Tanner:** None. **A.A. Hohorst:** None. **J. Westerman:** None. **E.B. Oleson:** None. **B.N. Greenwood:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.20/L19

Topic: F.03. Stress and the Brain

Support: Iowa Osteopathic Education and Research Foundation

Title: Sex differences in endocannabinoid release in response to voluntary wheel running

Authors: *V. MATHIS, M. MOHAMED, K. TEFFT, S. CLAYTON, L.-L. YUAN; Physiol. and Pharmacol., Des Moines Univ., West Des Moines, IA

Abstract: Consistent physical activity is associated with a wide range of physical and mental health benefits, while sedentary lifestyles pose increased risk for developing various chronic health conditions. The endocannabinoid (eCB) system has been implicated in both the immediate and long-term benefits of physical activity, and acute aerobic exercise has been found to induce eCB release into the circulation. Though the effect of exercise on eCB levels has been well studied, additional research is needed to elucidate the potential sex differences in the eCB system in response to physical activity. In the present study, we investigated the potential role of estrogen in the eCB system by adopting a unique rodent model of acute voluntary wheel running (VWR) and revealed intriguing sex differences. By artificially synchronizing the estrous cycles of female rats through ovariectomy (OVX) followed by acute estrogen supplementation, we identified significantly higher levels of serum eCBs in females compared to males including anandamide (AEA) and 2-arachidonoylglycerol (2-AG) immediately following a period of acute VWR. Recently, we refined our animal model in two ways. First, we administered luteinizing hormone-releasing hormone (LHRH) analogue to female rats to synchronize their estrous cycles physiologically. Second, we supplemented progesterone, along with estradiol, to OVX rats. These developments will allow for further exploration into the role of sex hormones in the eCB system. Research in the hormonal regulation of exercise behavior with greater precision could yield crucial insights into the mechanisms governing physical activity, ultimately refining strategies to promote regular exercise in humans.

Disclosures: V. Mathis: None. **M. Mohamed:** None. **K. Tefft:** None. **S. Clayton:** None. **L. Yuan:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.21/L20

Topic: F.03. Stress and the Brain

Support: Shaw Family Pioneer Award

Title: Intrinsically photosensitive retinal ganglion cells influence stress and reward

Authors: *H. L. MAHONEY[1], M. ARANDA[2], T. M. SCHMIDT[1];
[1]Neurobio., Northwestern Univ., Evanston, IL; [2]Dept. of Neurobio., Northwestern Univ., Evanston, IL

Abstract: Environmental light has a host of subconscious effects on physiology and behavior, most of which can be attributed to signaling from melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) to a wide range of targets in the brain. Intriguingly, many ipRGC targets integrate into stress and reward circuits, raising the possibility of interactions between these systems. To investigate the idea that ipRGC signaling might influence stress susceptibility and addiction liability, we examined nicotine-dependent behaviors

and the stress response in melanopsin knockout (mKO) mice, in which ipRGCs are present but lose their intrinsic photosensitivity.
To assess ipRGC contribution to the stress response, we exposed mKO mice to social isolation (SI) and acute swim stress, and measured serum corticosterone, adrenal weight, and markers for neurogenesis. Compared to group-housed controls, SI dampened the corticosterone response to an acute stressor in control mice, but this effect was completely absent in mKO mice. To investigate acute behavioral effects of nicotine treatment in mKOs, we used forced swim testing (FST), and trained a machine learning model to analyze depression-like behavior. We found that nicotine reduces immobility as expected in controls, but increases immobility in mKOs. We used nicotine conditioned place preference (CPP) and aversion (CPA) to examine reinforcement learning, which is central to the formation of addiction. While controls acquired both CPP and CPA as expected, mKOs failed to acquire conditioning. As a preliminary investigation of potential interactions between these systems, we then offered nicotine in a two-bottle choice test to SI and group-housed mice, and found that preference was altered in male group-housed (but not SI) mKOs.
To identify potential candidate mechanisms, we compared nicotine-dependent expression of c-fos. Nicotine produced lower c-fos expression in the lateral habenula and perihabenular nucleus of mKOs, as well as the ventrolateral geniculate nucleus (vLGN). We used inhibitory (Gi)DREADDs to silence the vLGN during nicotine CPP training sessions, resulting in a phenotype remarkably similar to mKOs, in which vLGN-silenced wild-type mice failed to acquire the conditioning.
Our preliminary data suggest that ipRGC signaling modulates the stress response and multiple nicotine-dependent behaviors, and possibly the sensitivity to nicotine itself. This newly identified ipRGC modulation of nicotine-dependent behaviors encourages the idea that manipulations of environmental light could eventually be used to enhance outcomes of existing cessation therapies.

Disclosures: H.L. Mahoney: None. **M. Aranda:** None. **T.M. Schmidt:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.22/L21

Topic: F.03. Stress and the Brain

Support: Wesleyan University startup

Title: Chemogenetic activation or inhibition of parvalbumin interneuron activity in the ventral hippocampus and changes to the neuroendocrine and behavioral impact of stress in male and female mice

Authors: *E. OWEN[1], S. WILSON[1], L. C. MELÓN[2], N. LEWIS[1];
[2]Biol., [1]Wesleyan Univ., Middletown, CT

Abstract: The ventral hippocampus plays a pivotal role in constraining the neuroendocrine and behavioral response to stress. Changes in parvalbumin interneuron function within this region has been linked to various psychiatric conditions associated with maladaptive regulation of stress reactivity. Sex differences in alcohol's effects on stress reactivity may involve a sex-specific degradation in parvalbumin interneuron function in the ventral hippocampus. We used PV-Cre mice and site-specific infusion of AAV5 particles from pAAV-hSyn-DIO-hM3D(Gq)-mCherry or pAAV-hSyn-DIO-hM4D(Gi)-mCherry to activate or inhibit parvalbumin interneurons across subregions of the ventral hippocampus of male (n's = 6-7) and female (n's=6-8) mice prior to their experience with a social stressor (trained same sex CFW aggressor mouse). Behavioral assessments followed using the elevated plus maze and bloods were sampled to permit corticosterone measurements at various time points post-stress. We found that activation of parvalbumin interneurons in the dentate gyrus significantly mitigated the sustained neuroendocrine response to this stressful event, evidenced by a significant decrease in corticosterone levels thirty minutes following social defeat. Interestingly, this manipulation did not affect behavioral responses in the elevated plus maze, suggesting a dissociation between neuroendocrine and behavioral adaptations to stress in this context. Inhibition of these interneurons caused minimal changes in neuroendicrone response to stress and no behavioral changes for females. Males, on the other hand, showed a 56.4% increase in their social-defeat stress associated anxiety-like behavior following inhibition of parvalbumin interneurons in the dentate gyrus. Further phenotypic profiling is necessary to understand whether sex-specific changes in the function that parvalbumin interneurons in the dentate gyrus of the ventral hippocampus reflects differences in social interaction between the experimental mouse and aggressor. The key findings highlight important differences that Gq versus Gi modulation of parvalbumin interneuron activity in this region has on the particular role that the ventral hippocampus plays in the stress circuit and the regulation of responsivity to social stress.

Disclosures: E. Owen: None. **S. Wilson:** None. **L.C. Melón:** None. **N. Lewis:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.23/L22

Topic: F.03. Stress and the Brain

Title: Emotional regulation, psychoaffective state, and academic stress in graduate students

Authors: *S. MORALES[1], T. CIBRIAN-LLANDERAL[2], Y. CAMPOS-USCANGA[3], L. LOPEZ-MERAZ[4];
[1]Inst. de Investigaciones Cerebrales, [2]Inst. de Neuroetologia, [3]Univ. Veracruzana, Xalapa, Mexico; [4]Univ. Veracruzana, Xalapa.

Abstract: Emotional regulation, essential for effectively managing emotional responses, is considered crucial in challenging academic environments. Emotional dysregulation,

characterized by a lack of understanding and dysfunctional management of responses, is associated with high levels of academic stress, an adaptive psychological process triggered by school demands. This study aimed to determine the relationship between academic stress, emotional dysregulation, anxiety, depression, and stress in graduate students. Data were collected using psychometric scales to assess academic stress (SISCO-SV21), anxiety, depression, stress (DASS-21), and emotional regulation (DERS-15) from 489 participants, with a distribution of 117 men and 372 women. Data normality was determined using kurtosis analysis, and descriptive statistics, Pearson correlation, and multiple regression analysis were employed. The significance level was set at $\alpha < 0.05$. The obtained data underwent statistical analysis with IBM SPSS Statistics 26. Significant associations were identified between negative affectivity, emotional dysregulation, and academic stress, particularly in academic stressors and stress symptomatology, with gender differences. In men, depression was related to higher academic stressors (p=.001), while in women, both anxiety (p=.004) and stress (p=.001) were associated with an increased perception of these stressors. Furthermore, it was observed that in men, higher emotional awareness correlated with a decrease in academic stress symptoms (p=.022), while in women, the use of emotional regulation strategies was linked to a reduction in such symptoms (p=.014). In women, higher levels of depression were related to less use of academic coping strategies (p=<.001), while higher emotional awareness was associated with greater adoption of these strategies (p=<.0001). The project received approval from the Research Committee of the Institute of Biological Research of the Universidad Veracruzana (registration 22-09) and the Ethics Committee of the Institute of Public Health of the Universidad Veracruzana (registration 22/2023).

Disclosures: S. Morales: None. **T. Cibrian-Llanderal:** None. **Y. Campos-Uscanga:** None. **L. Lopez-Meraz:** None.

Poster

PSTR472: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR472.24/L23

Topic: F.03. Stress and the Brain

Title: Biobehavioral investigations of cooking (BioCook): A novel approach to understanding the neural and psychosocial dynamics of cooking

Authors: N. M. FARMER[1], ***S. M. LAWLER**[2], R. HINGST[1], G. WALLEN[1];
[1]Natl. Inst. of Hlth., Clin. Ctr., Bethesda, MD; [2]Translational Biobehavioral Hlth. Disparities Br., NIH, Bethesda, MD

Abstract: Cooking is a dietary behavior that involves the utilization of executive function for planning, sensory environment awareness, and fine and gross motor usage. Psychological, social, and dietary benefits from cooking have been reported, as well as its utilization as a task-based therapy during neurorehabilitation. However, the existing literature is predominately based on

self-report and lacks rigorous scientific investigation with objective metrics to provide mechanistic understanding. The Biobehavioral Investigations of Cooking (BioCook) study offers a novel framework for investigating the intricate neural dynamics underlying cooking activities by examining the biological, psychological, and neural correlates of cooking behavior. Application of this research can further inform the utilization of cooking within the field of neurorehabilitation as well as develop interventions to address adverse psychosocial health. Primary aims seek to determine neural mechanisms in cooking tasks, explore relationships between neural and physiological correlates, and evaluate their predictive ability for psychological responses. The BioCook study will integrate multi-modal biometric and neurobiological measurements, including mobile EEG, heart rate variability monitoring, sensory system assessment, and salivary stress biomarker analysis, alongside enactive video-guided phenomenological interviews. The study will recruit 15 professional culinary participants and 15 non-professionals with low technical cooking skills and low frequency of cooking. Professional participants will be recruited first. Study procedures will occur when an age, gender matched non-professional cohort member is recruited to the study. All participants must be right-handed, have no concurrent neurological or psychological condition, including avoidance of cooking known as mageirocophobia. The primary objective of the initial phase of BioCook is to establish a robust methodology for real-time assessment, by evaluating the feasibility of multi-modal monitoring during cooking tasks. Subsequent studies will build upon this foundation to explore therapeutic interventions amongst diverse patient populations and alleviate cognitive and psychological burdens associated with home cooking.

Disclosures: N.M. Farmer: None. **S.M. Lawler:** None. **R. Hingst:** None. **G. Wallen:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.01/L24

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CONACYT Grant CF-2019-6390

Title: Genetic Contributions to Functional Connectome Topology in the Mexican Population

Authors: *I. ESPINOSA MÉNDEZ[1], J. DÍAZ-PATIÑO[1], D. RAMÍREZ GONZÁLEZ[1], T. V. ROMAN-LOPEZ[1], G. ROBLES RODRÍGUEZ[1], I. C. SÁNCHEZ[1], G. L. LICEA HAQUET[1], A. PIÑA HERNÁNDEZ[1], A. E. RUIZ-CONTRERAS[2], M. E. RENTERIA[3], S. ALCAUTER[1]; [1]Imagen, Inst. De Neurobiología, UNAM, Querétaro, Mexico; [2]Lab. Neurogenomica Cognitiva, Fac. Psicologia, Univ. Nacional Autonoma de Mexico, D.F., Mexico; [3]Queensland Inst. of Med. Res., Herston, Australia

Abstract: Functional Connectome (FC) variations result from genetic and environmental influences, which can be assessed through twin studies. However, there's a scarcity of such

studies in genetically admixed populations. Recent studies have explored the heritability of individual connections and network properties using graph theory. Here, we use Topological Data Analysis (TDA) to complement these studies by analyzing the Area Under the Curve (AUC) of Betti curves and the Minimum Spanning Tree (MST). Therefore, this study aims to characterize the genetic contributions to the AUC of Betti curves and compare the MST of Monozygotic (MZ) and Dizygotic (DZ) twins, providing new insights into the genetic and environmental factors influencing the FC.
We analyzed 108 pairs of twins (75 MZ and 33 DZ) from the Mexican twin registry (TwinsMX). Functional magnetic resonance images were acquired using a T2*-weighted echo-planar imaging sequence with a resting-state scanning duration of 10 minutes. High-resolution T1-weighted structural images were obtained using a turbo field echo sequence for coregistration. Data preprocessing was conducted using fMRIPrep 2023.0.1, and connectivity matrices were calculated using three different functional cortical parcellations (Schaefer, Glasser, and Gordon) with the XCP-D pipeline. Heritability estimates were obtained using a univariate ACE/ADE model, with sex and age included as covariates. To compare the MSTs across twins, a Poisson generalized linear model was used. For Betti-0 AUC, optimal models (per AIC) favored DE (except Schaefer, AE), with a genetic contribution ranging from 15%-33%. Betti-2 exhibited non-additive genetic contributions of 33% (Glasser) and 28% (Gordon); Schaefer showed no observed genetic influence. Betti-1 showed no heritability across atlases. Additionally, the MSTs, closely related to Betti-0, revealed a small, but significant effect between MZ and DZ twins in the Schaefer and Gordon atlases, showing that the MSTs are more similar between MZ twins than between DZ twins.
Genetic contributions are slightly lower than the average heritability of single connections (37%), yet bypasses the problem of multiple comparisons. Additionally, it provides a consistent genetic influence estimate of global FC. The differences in the MST between twins reveal a greater number of shared connections among MZ twins than DZ twins. Betti-0-related measures have proven effective in distinguishing between pathological groups and pubertal states. Thus, our findings suggest that these measures possess a significant genetic component, which could partially explain the variability observed in previous studies.

Disclosures: I. Espinosa Méndez: None. **J. Díaz-Patiño:** None. **D. Ramírez González:** None. **T.V. Roman-Lopez:** None. **G. Robles Rodríguez:** None. **I.C. Sánchez:** None. **G.L. Licea Haquet:** None. **A. Piña Hernández:** None. **A.E. Ruiz-Contreras:** None. **M.E. Renteria:** None. **S. Alcauter:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.02/L25

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Institutes of Health: R21NS123412
Sloan Fellowship
Pew Biomedical Scholar Award

Title: Altered behavioral and hemodynamic responses to a Stroop Task in patients with Long COVID.

Authors: *B. TAN[1], D. E. GOMEZ[3], L. D. LEWIS[1], E. BELDZIK[2], Z. YANG[4], S. ANAKWE[5]; [2]Cognitive Neurosci. and Neuroergonomics, [1]MIT, Cambridge, MA; [3]Massachusetts Gen. Hosp., Cambridge, MA; [4]Boston Univ. Grad. Program For Neurosci., Boston, MA; [5]Boston University, MIT, Newton, MA

Abstract: Long COVID, also referred to as Post-COVID Conditions, is associated with long-term symptoms beyond the acute infection stage. One of the most frequently reported symptoms is the persistence of fatigue and cognitive deficits. The neurological basis of these cognitive and arousal changes is not yet clear. In this study, we used high-resolution 7 Tesla fMRI during a cognitive control task in both healthy controls (n=13) and Long COVID patients (n=12). Participants performed the Stroop task to evaluate cognitive conflict processing by measuring responses to congruent (stimuli with matched color and word) and incongruent (stimulus conflict) cues. We first examined behavioral performance on the task, and found that the patients exhibited a stronger Stroop effect (reflected by their reaction time difference between congruent and incongruent trials) compared with the healthy controls (two-way ANOVA, p=0.015, adjusted for age). Patients also showed significantly slower reaction times to the incongruent trials, as compared to healthy controls (two-way ANOVA, p=0.019). We next examined fMRI responses to identify potential neural correlates of this behavioral effect. We analyzed the 10 regions of interest that were most strongly activated by the task, including the anterior cingulate cortex (ACC) which is known for its crucial role in processing the Stroop task and in arousal state modulation, precentral gyrus, and middle occipital cortex, consistent with prior studies. Though no significant group difference was observed in ACC, we found that in the left precentral gyrus, patients showed a greater BOLD signal change in response to incongruent trials (p=0.0068, uncorrected permutation test). In the 10 tested regions of interest, we also observed a stronger contrast effect in patients in the left precentral gyrus (p=0.0322, uncorrected permutation test) and left middle occipital cortex (p=0.0143, uncorrected permutation test). These results suggest that the slower cognitive control processing in patients may be accompanied by higher activation of cortical regions linked to conflict processing. Due to the small sample size, further data collection is needed to test whether the fMRI responses are consistently different across this network. These results show cognitive alterations in patients with Long COVID, and suggest that they may be linked to neurovascular dynamics that should be investigated further in larger studies.

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Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF Graduate Research Fellowship Program
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Title: A Tensor Decomposition Approach to fMRI Group Analysis: Detecting Resting State Brain Patterns in Cannabinoid Drug States.

Authors: *D. FELDMAN[1,2,3], M. D. PRIGGE[3], C. K. KING[3], J. MORGAN[3], L. SHAH[3], J. S. ANDERSON[3], J. B. KING[3];
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Abstract: While many studies examine long-term impacts of chronic cannabis use on neural connectivity, few studies have investigated the acute impacts of cannabinoid types, namely CBD and THC, on resting-state fMRI connectivity (Lorenzetti et al, 2023). To parse the distinct roles of THC, CBD, and their interactions in human brain function, we implemented a high order tensor decomposition to perform pattern discovery of resting-state neural connectivity data across 3 active cannabinoid drug states: CBD, THC, and CBD + THC. 37 Healthy individuals (18 F | age 30.4 ± 7.3) participated in 4 MRI scans at the University of Utah Imaging and Neurosciences Center following various cannabinoid administration. Each study participant received on four separate occasions (in random order, MRI scans separated by at least 1 month) an oral administration (oil) of 10 mg THC, 600 mg CBD, 10 mg THC + 600 mg CBD, or no drug (placebo condition). Data was processed as reported elsewhere (King et al. 2018), yielding connectivity matrices containing 64,980 edges between 361 unique cortical, subcortical, and cerebellar brain nodes. Data was recompiled into a 3-dimensional tensor with axes of connectivity edges, participants, and unique cannabinoid drug states. The resulting tensor underwent an unsupervised Tucker decomposition, thereby reducing data dimensionality to constituent drug-modulated patterns of brain connectivity. The decomposed component 1 serves as model validation representing a stereotyped brain connectivity matrix present under all drug conditions. In contrast, components 2 and 4 identify unique brain connectivity patterns associated with the acute presence of THC and CBD, respectively. Particularly, component 2 replicated previous findings of increased anti-correlation between the Default and Salience brain networks with acute THC administration (Kruskal-Wallis Test, $p < 0.001$ | Pairwise Dunn Test, $p < 0.001$, Bonferroni corrected). In contrast, component 4 yielded the inverse relationship, implying that CBD may subtly attenuate the effects of THC in overlapping brain connectivity networks. These results suggest that both THC and CBD administration yield salient effects on brain connectivity and that tensor decomposition may be a helpful method for characterizing first order effects of cannabinoids.

Disclosures: D. Feldman: None. **M.D. Prigge:** None. **C.K. King:** None. **J. Morgan:** None. **L. Shah:** None. **J.S. Anderson:** None. **J.B. King:** None.

Poster

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIMH Intramural Research Program (ZIAMH002783)

Title: Contribution of slow, brain-wide waves of activity to spontaneous thoughts during resting-state.

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Abstract: Subjects laying still inside an MRI scanner during resting-state functional MRI (rs-fMRI) are free to engage in different patterns of spontaneous thought. Simultaneously, their wakefulness levels are known to fluctuate as scanning progresses. Recent work demonstrates that it is possible to predict some aspects of such spontaneous thought (e.g., propensity to visual imagery, to explore their surroundings, to have positive/negative thoughts, etc.), as well as overall wakefulness levels based on functional connectivity (FC). In parallel, other work (Bolt et al. 2022) shows that approximately 30% of variance in rs-fMRI data is accounted for by three slow, brain-wide spatio-temporal waves of activity that were estimated using complex principal component analysis (cPCA). It remains unknown to what degree, if any, these waves of activity relate to subjects' state of mind (as determined by post-scanning reports of spontaneous thought and perceived wakefulness). To address this question, we used 471 rs-fMRI scans from the MPI Mind-Brain-Body dataset annotated with subject's reports of the content and form of their thoughts and wakefulness levels. We applied non-negative matrix factorization to the post-scan annotations (excluding wakefulness) and found two dominant spontaneous thought patterns (TP): TP1 which is characterized by positive thoughts in the form of images, and TP2 which corresponds to negative thoughts and a focus towards the surroundings. We used cPCA to estimate slow, brain-wide waves of BOLD activity specific to our sample. Finally, we used connectome predictive modeling (CPM) to assess how well we could predict scan-wise TP1, TP2, and wakefulness scores using FC estimated before and after regression of the top three cPCA components. Regression of the top three cPCA components significantly altered FC and resulted in statistically significant improvements in prediction accuracy for all targets (i.e., TP1, TP2 and wakefulness). Additionally, our results confirm the presence of slow waves of activity with similar spatiotemporal profiles to those previously reported in the literature. That said, in our sample the top three cPCA components only account for 6% of variance; likely due to different spatial smoothing strategies (Bolt el al. 2022: 5mm | us: no smoothing). These results suggest that these waves of activity estimated via cPCA are not directly linked to spontaneous thought patterns or wakefulness, as strong signatures of these aspects of subjects' subjective scanning experience remain present in the data after their regression.

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Poster

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Program #/Poster #: PSTR473.05/L28

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Assessing Brain Structure and Function in Adult Male and Female Mice: A Multimodal Magnetic Resonance Imagining and Behavioral Study

Authors: *M. BROOMFIELD[1], L. HERRERA PORTILLO[2], G. DESROSIERS-GRÉGOIRE[2], H. SCHULER[1], R. C. BAGOT[3], M. CHAKRAVARTY[4];
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Abstract: Sex-specific variations are prevalent across symptomatology, symptom severity, and age-of-onset within neuropsychiatric disorders[1]. However, neuroscientific and preclinical research in model systems has often been carried out only in male vertebrates or has neglected to examine sex-differences in treatment response or experimental design[2]. This may help explain why many treatments of neuropsychiatric disorders fail in clinical trials when scaled to human populations. To this end, we have limited understanding of sex-differences in the fundamental properties of brain structure and function, and commonly used behavioral paradigms in mouse models. Here, we seek to report these differences using *in vivo* functional and structural magnetic resonance imagining (rsfMRI,sMRI), and the open field test [OFT]. **Methods:** A total of 60 adult C57BL/6 mice (30/sex) underwent OFT followed by a sMRl and rsfMRI. To study behavioral data in detail, KeyPoint-Moseq (KPMS) was applied to uncover how different syllables (such as grooming, rearing, and pausing) might be expressed. Differences in brain volume were calculated with linear mixed effects models, corrected for multiple comparisons, and analyzed through deformation-based morphometry. Group-independent component analysis (ICA), dual regression (DR), and seed based connectivity (SBC) were applied to fMRI data. Brain-behavior relationships we examine using partial least squares (PLS). **Results:** OFT results revealed significant differences in mean velocity and total distance traveled with females having higher values ($t(58)=1.05$, $p=0.001$; $t(58)= -2.07$, $p=0.04$). Females showed a longer rearing time while males underwent sharp turns more frequently ($t(58)=-2.12$, $p=0.04$; ($t(58)=1.7$, $p=0.1$). After accounting for total brain size, regions such as the prefrontal cortex, somatomotor/ somatosensory regions, and the hypothalamus were larger in females, while males had a larger insula and olfactory bulb. Preliminary data in rsfMRI indicates females have higher amplitude for the somatomotor network. A correlation across the timeseries for all networks and seed ROIs indicates males have higher cortical-subcortical connectivity as well as higher interconnectivity across the cortex, while females express higher segregated network amplitude. These results

further validate findings previously reported across rats and humans[34]. **Conclusion:** To achieve a comprehensive understanding of how the brain works, integrating multiple imaging modalities is essential. We report sex differences across anatomical volume, functional connectivity, and behavioral outcomes in baseline adult mice.

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Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NARSAD YI Grant 25158

Title: Intrinsic network dynamics catalyze shifts in functional connectivity states of brain

Authors: *S. KANG[1], D.-J. KIM[2];
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Abstract: Dynamic functional connectivity (DFC) brain states, varying over time during rest or tasks, are crucial for understanding the brain's functional architecture and its adaptability to internal and external stimuli. While previous studies used static FC measures, recent DFC research highlights the brain’s dynamic nature and its cognitive and neuropsychiatric implications. Techniques like sliding window correlation and time-frequency analysis have revealed connectivity fluctuations. Edge time series analysis shows that high amplitude DFC co-fluctuations, aligned with peaks of BOLD signal variations, underlie static FC and define brain edge communities. However, the mechanisms driving these DFC changes and their broader impacts are still not fully understood. To bridge the gap in the field, we investigated DFC state changes using Human Connectome Project (HCP) resting fMRI data (N=100) and time-resolved phase coherence-based DFC measurements, less influenced by BOLD signal amplitudes. We defined 360 brain regions of interest (ROIs) and computed DFC at each time point as the leading eigenvector of the edges between ROI pairs, capturing the dominant connectivity pattern at that moment. By measuring the time-by-time similarity of DFC, we generated a DFC similarity time series, where we identified stable, transition, and switching periods of DFC. We found that the average interval between spontaneous DFC state-switching was about 32 seconds (SD=3.9). Graph theoretical analysis revealed that greater DFC dissimilarity correlates with lower modularity (switching < changing < stable; t=4.8, $p<10^{-5}$ and t=9.6, $p<10^{-15}$, respectively) and higher mean participation coefficient (switching > changing > stable; t=-2.0, $p<.05$ and t=-12.2, $p<10^{-20}$, respectively), suggesting that reduced within-modular clustering and increased diffuse cross-modular connections underlie DFC state transitions. Granger causality analysis confirmed

this relationship: the time series of graph theoretical measures (modularity and participation coefficient) of DFC, derived from sliding windows, predicted the DFC similarity time series. Conversely, the DFC similarity time series did not significantly predict the graph theoretical measures. Our findings emphasize the importance of dynamic network topology analysis for understanding spontaneous changes in brain states, potentially enhancing our knowledge of both normal and dysfunctional brain conditions.

Disclosures: S. Kang: None. **D. Kim:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

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Support: NIH: R01 DC020965
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Title: Developing a Movie Clip Database for Naturalistic Brain Mapping

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Abstract: There is a need for a repository of movie clips that can be used in naturalistic mapping of language and other high-order cognitive functions using fMRI and other brain mapping techniques. The development of a database of movie clips, validated by reliable emotional elicitation, is a crucial first step in developing a naturalistic fMRI paradigm which uses a movie-watching condition for comprehensive brain mapping. This study aims to determine which types of clips are most effective, reliable and stable in eliciting emotional reactions across subjects, and are therefore suitable for naturalistic stimulation of language and emotion networks during fMRI brain mapping for presurgical planning.
Healthy subjects without neurologic or mental health conditions were recruited and screened leading to 97 subjects (58 females, age range: 18-60 years old) being enrolled into this study. Subjects were asked to participate in 1 or 2 movie watching sessions, viewing a total of 22 movie clips (2-7 min), during which they were asked to provide dynamic ratings of valence and arousal of their emotion reactivity to the clips. Subject dynamic ratings were collected using CARMA, a media annotation program that collects continuous ratings while displaying audio and video files. Subjects rated emotional valence on a continuous scale from -4 (very negative) to +4 (very positive). After each clip, subjects answered questions about movie clarity, familiarity, and three

comprehension questions about the content of the clip. They also provided holistic ratings of the clip's emotional salience and affective dimensions using the short version of the Positive and Negative Affect Scale short form (PANAS).
The clips evoked broad emotional valence and specific emotions which were confirmed by analyses of the distribution of dynamic and holistic ratings. For all clips, the dynamic ratings were normally distributed. The inter-rater reliability in dynamic ratings, calculated as the average-measures consistency intraclass correlation (ICC), was above 0.90. A variance decomposition analysis indicated that the largest sources of variance in dynamic valence ratings were the movie clip (38.7%), clip by rater interaction (19.3%), and clip segment (13.4%), whereas rater on its own accounted for only 5.1% of the variance. Comprehension questions yielded an average of 95.77% accuracy across all clips.
This study developed a diverse movie database with consistent emotional elicitation across subjects. These stimuli will be used to develop a movie fMRI paradigm for comprehensive brain mapping and could be useful for investigation into other neurologic or mental health conditions.

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Poster

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Title: Exploring the alterations in functional connectivity in indivisuals with self-harmed behavior

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Abstract: Suicide is one of the major causes of global death, with approximately 10 per 100,000 individuals dying by suicide each year. Most research on self-harmed behavior and suicide attempts has focused on individual experiences and developmental backgrounds, lacking biomarkers. Brain networks and functional connectivity (FC) retrieved from resting-state functional magnetic resonance imaging (rs-fMRI) have been identified as critical biomarkers among mental states. Previous studies have indicated that self-harmed behavior was correlated with aberrant functional networks, but times and intervals were less mentioned. In this study, we aimed to clarify the association between self-harmed behavior and FC. Individuals with self-harmed behavior including times, intervals and extent of ideation were selected based on the mental health questionnaire in the UK Biobank. Rs-fMRI data was from UK Biobank and was preprocessed with DPABI toolbox. FC matrices were constructed using Pearson's correlation coefficient between blood oxygen level dependent signal among brain areas parcellated by Anatomical Automatic Labeling Atlas. A general linear regression model was employed to identify significant FC correlated with the times and intervals of self-harmed behavior and the extent of self-harmed ideation. False discovery rate corrections were performed for multiple comparisons. Total of 1,120 participants were included in this research. Individuals were on average age of 51.80 (S.D. = 7.16) years old, with 77.9% of them being female. Despite no significant differences found after corrections, the results showed trends of positive correlations of FC between the frontal lobe and cuneus, and between the frontal lobe and occipital lobe as increasing self-harmed times. Individuals with self-harmed behavior more than one year ago showed trends of negative correlations of FC between frontal lobe and temporal lobe, as well as between the middle frontal gyrus and rectus gyrus in the frontal lobe. Individuals with the intention to end their lives showed trends of negative correlations of FC between the para-hippocampal gyrus and amygdala, but positive correlations of FC between the right caudate and other brain regions. This research revealed that times, intervals of self-harmed behavior, and the extent of self-harmed ideation were correlated with the strength of FC. Further research is needed to clarify the relationship between self-harmed behavior and FC, ultimately contributing to a deeper understanding of the etiology of self-harmed behavior.

Disclosures: J. Lin: None. **A. Yang:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Functional analysis of simultaneous spinal cord-brain fMRI during finger movements in healthy and dystonic subjects.

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Abstract: Background: Focal task-specific dystonia (FTSD) is one of movement disorders that can interfere with specific movements involved in highly trained complex tasks such as writing, playing an instrument, and doing sports. One of the main pathophysiological features reported for FTSD is a loss of inhibition in the motor and somatosensory cortices, as demonstrated by neurophysiological studies. This feature reflects the hyperactivity seen in functional neuroimaging studies in FTSD. One electrophysiological paper reported the disinhibition of the spinal reflex circuits in patients with FTSD. However, no imaging papers showed the spinal cord hyperexcitability directly. We performed Functional Analysis of unilateral finger movement using simultaneous Spine and Brain fMRI (FASB) to investigate whether patients with FTSD have spinal cord hyperactivity. Methods: Eleven healthy pianists (HP) and fourteen dystonic pianists (DP) participated in the study. Previous studies pointed to greater intra-subject variance of keystroke and key release timing when patients with musician dystonia performed a simple passage on piano. Prior to the fMRI experiment, we recorded variations of inter-keystroke interval (IKI) and inter-keyrelease interval (IRI). Then, we observed neural activity in the brain and spinal cord while they performed simple unilateral finger movement tasks inside the 3T-MRI scanner (Siemens MAGNETOM Skyra Fit). FASB was performed using SPM12, FSL, spinal cord toolbox, and AFNI. We calculated brain and spinal cord activity related to unilateral simple finger movements (non-symptom-provoking) and compared them between healthy and dystonic pianists. Statistical significance was set at uncorrected $p < 0.001$ for the brain and $p < 0.05$ for the spinal cord. Results: Both IKI and IRI variabilities were significantly greater in the DP group than in the HP group. FASB revealed that both groups showed activity in the primary motor cortex and the putamen contralateral to the moved fingers, as well as the ipsilateral cerebellum and the anterior horn of the spinal cord. Activity in these brain regions showed comparable between the DP and the HP groups except in the spinal cord. The finger movement tasks activated the anterior horn in the C7 segment of the cervical spinal cord in both groups. Note higher activity in this region in the DP than the HP group. Conclusion: Our results suggest abnormal control of finger movements in the patients even in a simple experimental setting. FTSD showed higher activity in the cervical spinal cord segment innervating intrinsic hand muscles, which involved in a simple finger motor task used in the present investigation.

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Poster

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Title: Functional Magnetic Resonance Imaging of spinal cord during execution and imagery of plantar and dorsiflexion execution in human.

Authors: *Y. MIYAZAKI[1,2], K. TSUJIMOTO[3], S. VAHDAT[4], K. SAJIMA[3], R. TOKIMURA[3], S.-Y. TANAKA[3], D. NISHIDA[1,2], T. HARA[1], T. TSUJI[5], M. ABE[3];
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Abstract: Background In post-stroke rehabilitation, improving gait function is crucial as it directly impacts quality of life. Previous studies on decerebrate cats have indicated the presence of Central Pattern Generator (CPG) in the spinal cord, which autonomously generates gait like muscle activities independent of the brain. Consequently, many medical professionals hypothesize that post-stroke rehabilitation can enhance gait function by targeting the spinal cord CPG. Stimulation of the spinal cord at the 12th thoracic vertebra has been shown to activate gait-like muscle activities, suggesting the existence of CPG in humans around the 12th thoracic vertebra. However, this electrical stimulation is passive and invasive, posing challenges for assessing spontaneous CPG activation non-invasively in clinical practice.The purpose of this study is to establish an evaluation system for spinal cord CPG during the execution and imagery of plantar and dorsiflexion movements using spinal cord functional Magnetic Resonance Imaging (sc-fMRI), which can non-invasively assess spontaneous spinal cord neural activity.
MethodTwo healthy males (ages 24 and 30) were participated in this study and instructed to perform plantar dorsiflexion execution and imagery of the right ankle joint. Images were obtained between the 10th thoracic spine and 2nd lumbar spine using 3.0T MRI (Skyra Fit, Simens). The imaging data were analyzed using FSL, Spinal cord toolbox, and SPM12 to calculate spinal cord activities.
ResultAround 5th lumbar spinal cord level, subject 1 showed right ventral dominance of spinal cord activity during both execution and imagery, but not in subject 2. Around the second lumbar spinal cord level, both subjects showed bilateral dorsal spinal cord activity during motor execution. Subject 1 also showed bilateral spinal nerve activity during motor imagery.
DiscussionPlantar dorsiflexion movements of the ankle joint are innervated in the region between 4th lumbar spinal cord and 1st sacral spinal cord. Spinal cord activities around the 5th

lumbar spinal cord were unilateral on the right and is thought to be due to plantar dorsiflexion movements of the right ankle joint. Since the 12th thoracic vertebra is the region stimulated in the previous study and the second lumbar spinal cord region, bilateral spinal nerve activity at this level may reflect CPG activity. The limitation of this study is the small number of subjects, so a second analysis with more subjects is needed in the future. **Conclusion**Bilateral blood flow changes suggestive of spinal cord CPG were observed with plantar dorsiflexion movements.

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Poster

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Support: CREST2024

Title: Spinal cord neural activity is involved in modulating μrhythms during motor imagery

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Abstract: The mu rhythm is a brain rhythm in the 8-12 Hz range originating from motor-related areas of the cerebral cortex. The mu rhythm exhibits a power attenuation during motor imagery. It is already known that various areas of the cerebral cortex are involved in μ rhythmsmodulation. However, based on insights from research on spinal cord injury patients, we hypothesized that the spinal cord neural activity is involved in μ rhythms modulation. Therefore, this study aimed to elucidate spinal cord neural activity during motor imagery using fMRI and reveal the correlation between μ rhythm and spinal cord neural activity.Twenty-seven healthy adults (17 females, mean age 27.8 ± 5.2 years) were measured as participants. Participants performed a right or left hands motor imagery task in the scanner. Simultaneous EEG-fMRI recordings were obtained during the tasks. Preprocessing of EEG and fMRI data was performed using EEGLAB, FSL, SPM, and the Spinal cord toolbox. We calculated power values in the alpha frequency band of the motor cortex area. We investigated cortical and spinal cord neural activity during motor imagery, regions where spinal cord neural activity increases with attenuation of μ rhythms, and functional connectivity between the cerebral cortex and spinal cord. Additionally, we calculated correlation between the rate of change in μ rhythm power values and the strength of functional connectivity between the cerebral cortex and spinal

cord.Cerebral cortex activity was observed in the parietal lobe and premotor cortex areas (Uncorrected, p <0.001). Spinal cord neural activity was observed in the anterior and posterior horns at the C6-7 vertebral level (Uncorrected, p <0.001). Along with the attenuation of μ rhythm during motor imagery, activity was observed in the anterior and posterior horns of the C6-7 vertebral level (Uncorrected p <0.001). Functional connectivity was observed between the anterior horn and the right premotor cortex, the right primary somatosensory cortex. On the other hand, the posterior horn was observed functional connectivity with the premotor cortex and the right inferior parietal lobule. Furthermore, the strength of functional connectivity between the posterior horn and the inferior parietal lobule showed a positive correlation with the rate of μ rhythm changes. This study is the first to capture spinal cord neural activity during motor imagery using fMRI and to discover the involvement of spinal cord neural activity and functional connectivity between the cerebral cortex and spinal cord in μ rhythms modulation.

Disclosures: K. Tsujimoto: None. **R. Tokimura:** None. **K. Sajima:** None. **Y. Miyazaki:** None. **S. Vahdat:** None. **M. Abe:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.12/L35

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH (U19NS123716)
Wellcome Trust (223144)

Title: Modulation of brainwide activity by arousal

Authors: *A. LANDEMARD[1], M. KRUMIN[1], C. REDDY[2], K. D. HARRIS[1], M. CARANDINI[1];
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Abstract: Introduction. Mice spontaneously go through episodes of low or high arousal, revealed by locomotion, pupil dilation, and whisking. These episodes are associated with activation of neuromodulatory systems and dramatically affect cortical activity. How do they affect the rest of the brain? Do they correspond to specific brainwide patterns of activity?
Methods. To record activity in multiple brain regions we used functional Ultrasound imaging of hemodynamic activity in head-fixed mice that were free to run on a wheel. We then used optogenetic stimulation of cholinergic neurons in the basal forebrain to causally manipulate the arousal system.
Results. Locomotion onset was typically preceded by whisking and was associated with a stereotyped brainwide sequence of activation over the course of seconds, from ventral regions such as midbrain and hypothalamus up to the cerebral cortex and hippocampus. On the other

hand, whisking in the absence of locomotion was associated with a widespread and simultaneous activation followed by a suppression, with different amplitudes in different regions. Optogenetic activation of cholinergic neurons led to an increase in behavioral arousal, as seen by an increase in whisking and pupil dilation. It also caused changes in brainwide activity, with activation of thalamic and midbrain nuclei followed by suppression in particular in the hippocampus. These effects were overall stronger when the mouse was in a low-arousal state before stimulation onset. Conclusions. We conclude that locomotion and whisking correlate with activity in the whole mouse brain, not just in the cortex, and do so at multiple timescales and with distinct contributions. The activation of cholinergic neurons triggers a sequence of activations and suppressions involving a similar network of brain regions, suggesting a possible common mechanism.

Disclosures: A. Landemard: None. **M. Krumin:** None. **C. Reddy:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.13/L36

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Functional ultrasound in drug discovery

Authors: *S. STANKOWICZ[1], K. S. GHAEMI[2], M. PATROVANIE[3], E. MOROZOVA[3], E. FULLWOOD[3], S. GEISLER[3], R. SOPKO[4], C.-C. (. LIU[5], A. GHOSHAL[3];
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Abstract: Functional ultrasound technology holds great potential in neuroscience drug discovery. Translating preclinical work in rodents to the clinic remains a significant challenge, including readout of pharmacodynamic responses, proving target engagement in deep brain regions, and demonstrating preclinical proof of biology. Functional ultrasound can help bridge these gaps with whole-brain recordings in awake or anesthetized mice, at a lower cost than MRI and with higher coverage than electrophysiology or calcium imaging. Functional ultrasound has tangible applications in neurodevelopmental, vascular, and neurodegenerative disorders. Vascular reactivity can be measured in the clinic using a vasodilator, acetazolamide. We have used functional ultrasound to investigate effects on vascular reactivity in a genetic model of human disease, enabling reverse translation of this phenotype. This platform will continue to aid drug development with the hope that similar readouts can soon be undertaken in human clinical trials, further increasing the probability of technical and regulatory success for devastating human neurological diseases.

Disclosures: S. Stankowicz: A. Employment/Salary (full or part-time):; Biogen. **K.S. Ghaemi:** A. Employment/Salary (full or part-time):; Biogen. **M. Patrovanie:** A. Employment/Salary (full or part-time):; Biogen. **E. Morozova:** A. Employment/Salary (full or part-time):; Biogen. **E. Fullwood:** A. Employment/Salary (full or part-time):; Biogen. **S. Geisler:** A. Employment/Salary (full or part-time):; Biogen. **R. Sopko:** A. Employment/Salary (full or part-time):; Biogen. **C.(. Liu:** A. Employment/Salary (full or part-time):; Biogen. **A. Ghoshal:** A. Employment/Salary (full or part-time):; Biogen.

Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.14/L37

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Exploring vascular pathologies in neurodegeneration: A novel functional ultrasound approach in the STZ-induced diabetes model

Authors: M. MUTIKAINEN, R. IMMONEN, L. RAUHALA, *J. OKSMAN, **A. SHATILLO**, S. BÄCK;
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Abstract: Vascular pathologies, such as cerebral amyloid angiopathy (CAA), are common in many neurodegenerative and neurological disorders. Validating affordable animal models and testing platforms for such pathologies is crucial for developing novel therapeutics. In this work, we established and characterized the streptozotocin (STZ) model of diabetes in rats, which manifests both neuronal and vascular pathology, such as retinopathy and global vascular reactivity impairment.
The aims were 1) optimization of the model by comparing animal welfare and phenotype between multiple protocols (doses, fasting formulations of the STZ), and 2) evaluation of a novel non-invasive and sensitive neuroimaging modality - functional ultrasound (fUS).
To establish and optimize the model, we utilized two cohorts of male Wistar rats (n=28) split into seven distinct groups. Each group received a single intravenous injection of either STZ at a dose of 50 mg/kg or 65 mg/kg or a vehicle control, with or without prior 12-h fasting period and different solution preparation (anomer-equilibrated or non-anomer-equilibrated). Dosing was followed by a management protocol that included ad libitum access to 20% glucose (200 g/L) solution for 24 h to mitigate acute hypoglycemia. Body weight and food consumption were recorded daily for the first 7 days (D0-D6) and then twice weekly.
Serial blood sampling occurred on days 1, 5, and 7 to establish acute responses to STZ, with subsequent fortnightly assessments to monitor chronic glucose, insulin, and c-peptide levels via ELISA.
In-life whole blood samples were collected on study days 1 (D1), 5 (D5), and 7 (D7) to monitor blood glucose levels and confirm model induction. Rats with glucose levels ≥ 300 mg/dl (16.7 mmol/L) were considered diabetic and were followed up with weekly glucose blood sampling,

insulin, and c-peptide levels from D14 to 10 weeks after the STZ challenge.
At ~10 weeks after the STZ challenge, the animals underwent functional ultrasound (fUS) imaging using the Iconeus One system. The imaging protocol included structural scans (contrast-enhanced 3D imaging of the periorbital and ocular vasculature and ultrasonic localized microscopy of the eye's cross-section) and functional imaging (dynamic blood flow assessment and visual stimulation responses) under medetomidine anesthesia.
This study successfully established a rat model of diabetes using STZ, incorporating various in-vivo readouts and functional ultrasound imaging. This platform holds promise for drug discovery and efficacy projects, not only for diabetic pathology but also for neurovascular disorders in CNS diseases.

Disclosures: M. Mutikainen: A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **R. Immonen:** 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. **J. Oksman:** A. Employment/Salary (full or part-time):; Charles River Discovery Research Services. **A. Shatillo:** 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

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.15/M1

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: KAKENHI JP21H03809
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KAKENHI JP23H05450
Uehara Memorial Foundation for Life Sciences

Title: Optimization of a small and high signal-to-noise ratio functional brain imaging device using self-resetting pixels

Authors: *K. SASAGAWA[1], S. IWAKI[2], Y. SUNAGA[3], Y. OHTA[4], H. TAKEHARA[1], M. HARUTA[5,6], H. TASHIRO[1,7], J. OHTA[8];
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Abstract: Miniature CMOS image sensors enable the realization of compact imaging devices for measuring brain function under freely moving conditions [1,2]. In optical measurement of brain

function, it is sometimes required to irradiate light of sufficiently high intensity and detect slight luminance changes. However, general image sensors could not handle high intensity light due to pixel saturation. Therefore, image sensors with larger pixels and larger pixel capacity have been conventionally used in such cases, but it was difficult to apply them to the measurement under freely moving condition. To address this issue, we have proposed an image sensor that can achieve a high signal-to-noise ratio despite its small size by increasing the effective pixel capacitance with a self-resetting pixel that avoids pixel saturation [3]. We have demonstrated that under appropriate conditions, an SNR of more than 70 dB can be achieved with a noise level of about 0.03%. However, when the light intensity at the observation point coincides with the conditions under which self-resetting occurs, the noise rises significantly and the SNR is reduced. In this study, we optimized the conditions for reducing SNR and investigated a method to achieve a high signal-to-noise ratio by reading each pixel twice per frame using nondestructive readout, which is a feature of CMOS image sensors. In the case of a single readout, the self-reset time had to be as short as possible. In contrast, in the proposed method, even if one of the two readouts overlaps with the self-reset condition, the other can be made complementary to avoid this condition. Therefore, the self-reset time can be set to the condition that minimizes the noise generated by the self-reset. This method solves the problem of conventional self-resetting image sensors and achieves small dimensions and a high signal-to-noise ratio that can be mounted or implanted in the head of a mouse. [1] J. Ohta *et al.*, Proc. IEEE, vol. 105, 158-166, 2016.[2] Y. Sunaga *et al.*, IEEE Access, vol. 9, pp. 55871-55878, 2021. [3] T. Pakpuwadon *et al.*, Front. Neurosci., 15667932, 2021.

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Poster

PSTR473: Functional Imaging of Brain Blood Flow, Metabolism, and Homestasis

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR473.16/M2

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NFRFE-2020-01351
Optica

Title: Characterizing brain dependant ultra-weak photon emissions for non-invasive functional neuroimaging

Authors: *J. MEIKLE, V. L. HOSSACK, N. ROULEAU, N. J. MURUGAN;
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Abstract: Endogenous light emissions, or biophotons, have been detected from several tissues including those of the nervous system, and may serve as biomarkers for non-invasive functional neuroimaging. Biophotons emissions (BPE) are spontaneously emitted by cells and are coupled

to their metabolic state with associated wavelengths centering on the visible spectrum (200 nm to 800 nm). Since neurons express non-visual opsins, neurotransmitters, flavins, and other molecules that are photoactivated by the same wavelengths, it has been proposed that neural systems exchange and transduce optical signals. Neural-dependent BPE studies show increasing prevalence in literature but suffer from methodological inconsistencies, highlighting the necessity for standardized devices and signal processing techniques. We have designed an exploratory study to characterize neuronal BPEs, their relationship with electric field oscillations, and how they might be evoked using sensory stimuli, informing the design of a novel brain BPE device toward non-invasive brain state detection. In this study, 30 participants were recruited to sit quietly in a hyper-dark chamber while voltage fluctuations and BPEs were measured over the surface of their scalps using quantitative electroencephalography (qEEG) and photomultiplier tubes (PMTs), respectively. A PMT was also placed elsewhere in the chamber, away from the participant, to isolate brain-relevant photonic signals.. Baseline recordings with eyes open and closed were obtained before and after a 2-min exposure to an auditory stimulus, which was a pulsed pure tone (165 BPM), delivered via a digital metronome. We hypothesized that qEEG differences associated with baseline conditions (e.g., eyes closed alpha) and the auditory stimulus would correlate with BPEs over the occipital and temporal lobes, respectively. Preliminary analyses suggest qEEG alpha (7Hz - 14 Hz) power and alpha peak frequency were significantly altered between baseline and auditory stimulation conditions. BPEs over the occipital and temporal lobes were negatively correlated with qEEG features and displayed greater signal entropy relative to background BPE sources. Sex differences in average BPE counts based on brain state, and brain-region were also observed. The results from this study lay the groundwork to (a) characterize brain BPE as light-based biomarkers for subtle brain state changes and (b) develop a platform to promote their utility in predicting cognitive states in real time.

Disclosures: J. Meikle: None. **V.L. Hossack:** None. **N. Rouleau:** None. **N.J. Murugan:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.01/M3

Topic: F.08. Food and Water Intake and Energy Balance

Title: A CNS-targeted gene therapy for the treatment of severe pediatric obesity

Authors: C. JIN[1], N. FABELA[1], A. LETTKO[1], J. BASTIAANS[1], D. LEE[1], E. HERNANDEZ[1], T. NGUYEN-VU[2], C. LIU[1], *J. SULLIVAN[1];
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Abstract: In the ventromedial hypothalamus, the leptin-proopiomelanocortin pathway interprets energy signals from the periphery to initiate feeding or fasting through two opposing neuronal populations. In a fed state, elevated leptin signals a decrease in food intake via the release of

brain derived neurotrophic factor (BDNF) from melanocortin 4 receptor (MC4R) expressing neurons. Loss-of-function mutations along this pathway, including in MC4R or BDNF, cause severe obesity in humans. MC4R deficiency leads to a severe form of early-onset pediatric obesity that is characterized by an increased drive to eat and impaired satiety. Hyperphagia and food-related distress have been reported in patients as young as 8 months old. Current therapeutic approaches such as bariatric surgery and glucagon-like peptide 1 (GLP1) agonists do not result in significant, durable treatment for persons with MC4R deficiency. MC4R agonists are being developed, but this approach will not benefit patients with homozygous mutations. Therefore, there remains a need to develop a therapeutic that results in healthy weight loss that can be maintained throughout life. With this aim, we developed an adeno-associated virus (AAV)-based gene therapy to deliver BDNF to the ventromedial hypothalamus to treat patients with MC4R deficiency. Here, we show that our optimized BDNF gene therapy, designed by altering various cis-regulatory components, achieves significantly higher expression compared to a previously published construct. In head-to-head comparisons in primary mouse cortical neurons and various immortalized neural cell lines, the optimized vector achieved 4-fold greater expression. As a demonstration of our synthetic promoter, expression of a fluorescent protein was as strong as the CAG promoter while off-target expression in the liver and heart was much lower, highlighting the specificity of our promoter. Furthermore, AAV-mediated delivery of our optimized BDNF gene therapy to the hypothalamus caused significant weight loss in a diet-induced obesity (DIO) mouse model within 21 days. Our BDNF gene therapy expresses 143-fold greater than basal levels of BDNF *in vivo*, which is in excess of the 10-fold increase required to prevent weight gain in the DIO model. By designing a highly expressing BDNF gene therapy, we can drive efficacy at lower viral vector doses and potentially lower immune responses and decrease safety risks. Taken together, these results indicate a potent and effective gene therapy for the treatment of patients with MC4R deficiency.

Disclosures: C. Jin: A. Employment/Salary (full or part-time):; MeiraGTx. **N. Fabela:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MeiraGTx. **A. Lettko:** A. Employment/Salary (full or part-time):; MeiraGTx. **J. Bastiaans:** A. Employment/Salary (full or part-time):; MeiraGTx. **D. Lee:** A. Employment/Salary (full or part-time):; MeiraGTx. **E. Hernandez:** A. Employment/Salary (full or part-time):; MeiraGTx. **T. Nguyen-Vu:** A. Employment/Salary (full or part-time):; MeiraGTx. **C. Liu:** A. Employment/Salary (full or part-time):; MeiraGTx. **J. Sullivan:** A. Employment/Salary (full or part-time):; MeiraGTx Employee.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.02/M4

Topic: F.08. Food and Water Intake and Energy Balance

Title: Mapping Brain Regions Associated with Obesity: Insights from Volumetric Analysis and Functional Connectivity

Authors: X. WANG[1], Y. NAKAMURA[2], ***T. IKUTA**[3], *T. IKUTA[4];
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Abstract: The neural substrates underlying obesity remain incompletely understood. In this study, we endeavored to delineate brain regions exhibiting significant associations with Body Mass Index (BMI), followed by an exploration of their functional connectivity patterns. Leveraging T1-weighted and resting-state functional MRI data from a cohort of 327 subjects from the enhanced Nathan Kline Institute-Rockland Sample, we initially probed the relationship between brain volume and BMI employing FSL-VBM. Subsequently, seed-based functional connectivity analyses were conducted for the identified regions. Our findings showed positive volumetric associations between BMI and the right and left occipital cortex, left cerebellum, right nucleus accumbens, and left putamen. Furthermore, functional connectivity analyses showed significant connections between the right nucleus accumbens and left putamen with the parahippocampal gyrus, both positively correlated with BMI. These results suggest a putative role of striatal regions in modulating body weight, with such influence potentially mediated through striatal-parahippocampal connectivity. Notably, the parahippocampal gyrus, known for its responsiveness to food-related stimuli, emerges as a pivotal node in this reward-food circuitry. Insights from this study shed light on the neurobiological underpinnings of body weight regulation, underscoring the potential therapeutic relevance of modulating striatal-parahippocampal connectivity to ameliorate obesity.

Disclosures: X. Wang: None. **Y. Nakamura:** None. **T. Ikuta:** None. **T. Ikuta:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.03/M5

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant ES021624
OU VPRP Faculty Investment Program

Title: The Neural efficiency score: Quantifying the relationship between work accomplished and energy expended using reaction times and EEG

Authors: *M. J. WENGER[1], J. T. TOWNSEND[2], S. F. NEWBOLDS[3], M. P. DUNGAN[4];
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Abstract: The brain expends energy in the performance of mental work but there have been limited attempts to link measures of cognitive work with measures of energy expended. We have suggested that the hazard function of the reaction time (RT) distribution, *h(t)*, can be interpreted as an instantaneous measure of the amount of work performed. We here suggest that the global field power (GFP) of electroencephalographic (EEG) data can be interpreted in terms of brain energy expenditure. Forming a ratio of *h(t)* and the GFP gives a ratio that we refer to as the *neural efficiency score* (NES). To demonstrate that the NES can be interpreted in terms of neural efficiency, we need to show that GFP can be related to metabolic energy expended. To do this, we analyzed unpublished data from a previous study (Wenger, DellaValle, Murray-Kolb, & Haas, 2017) in which we collected simultaneous behavioral, EEG and metabolic data (O_2 consumed and CO_2 expired) during the performance of a cognitive task that was systematically varied in difficulty. We show that, in these data, GFP and energy expended are regularly related and that both track variations in workload. We then used unpublished data from another previous study (Newbolds & Wenger, 2024) in which two groups of women, one iron sufficient (IS) and a second iron deficient and non-anemic (IDNA), performed a contrast detection threshold task with concurrent EEG. We used the RTs from trials on which correct responses were made to estimate *h(t)* and we used the EEG data from the same trials to calculate the GFP, and from these two components we formed the NES. We found that *h(t)* was reliably higher for IS than for IDNA women but converged for the longest RTs, suggesting that for at least a portion of the RT distribution, IS women were accomplishing more work than IDNA women. This ordering was reversed in the GFP data, suggesting that IDNA women were expending more neural energy to accomplish their perceptual work than were IS women. Combining these variables in the NES showed that IS women had a higher level of neural efficiency than did IDNA women and this was true across the range of RTs. The components of the NES were regularly related to biomarkers indicative of both the body's iron stores and iron's role in O_2 transport, and that the NES was reliably related to thresholds. Finally, we showed that the relationship between iron levels and thresholds was completely mediated by neural efficiency. The results support the plausibility of the NES as an indirect measure of the relationship between the amount of mental work accomplished and the amount of brain energy expended as well as the general applicability in studying cognition in both normal and perturbed physiological states.

Disclosures: M.J. Wenger: None. **J.T. Townsend:** None. **S.F. Newbolds:** None. **M.P. Dungan:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.04/Web Only

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Z.280152092015-HPC(EMR)-AYUSH

Title: Yoga improves cognition-related cerebrovascular and prefrontal hemodynamic functioning in type 2 diabetes

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Abstract: Context: Research has shown a link between type 2 diabetes (T2DM) and cognitive decline, which can result in dementia and Alzheimer's disease. **Aim:** The aim of this study was to examine the possible effects of three months of yoga practice on the oxygenation of the prefrontal cortex (PFC), the middle cerebral artery cerebrovascular reactivity, and cognitive abilities in people with type 2 diabetes. **Materials and Methods:** Seventy-five patients were randomly assigned to either the yoga group (n = 38; seven females; mean age 52.95 (8.20) years) or the waitlist control group (n = 37; six females; mean age (standard deviation) 49.62 (10.94) years). A screening was performed on these subjects using the Montreal Cognitive Assessment, and those who scored lower than 26 were disqualified from the study. We used transcranial doppler and functional near-infrared spectroscopy to look at the blood flow in the brain and the activity of the prefrontal hemodynamic system while the people were at rest and while they were thinking. The participants in the yoga group were given an intervention for a period of three months, and evaluations were carried out at three different points: at the beginning (after one week), at the middle (after six weeks), and at the end (after twelve weeks). **Results:** Following a 12-week intervention, the yoga group's members demonstrated increased working memory task accuracy and response time in a 2-back condition ($p<0.05$ and $p<0.01$, respectively), as well as better Corsi Block Tapping task scores ($p<0.001$). Also, after 12 weeks of yoga, there were higher peak systolic velocity ($p<0.001$), mean blood flow velocity ($p<0.001$), end-diastolic velocity ($p<0.001$), and breath-holding index ($p<0.05$), which shows changes in the middle cerebral artery. In the 12th week, the yoga practitioners group had increased oxygenation at the dorsolateral, dorsomedial, ventromedial, and orbitofrontal PFC ($p<0.05$) in comparison to the control group. Also, people in the yoga group had more oxygen in the dorsolateral PFC ($p<0.05$) compared to before and more oxygen in the ventrolateral, orbitofrontal, ventromedial, and dorsolateral PFC ($p<0.05$) compared to people in the control group during the 2-back working memory task. **Conclusion:** The results suggest that yoga practice can improve cerebral blood flow through the middle cerebral artery and hemodynamic activities in the prefrontal regions of patients with type 2 diabetes, which may help improve cognitive functions.

Disclosures: D. Singh: None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.05/M6

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: The impact of weight on intermittent fasting

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Abstract: Introduction: Approximately 78 million adults in the United States are impacted by obesity. While caloric reduction is commonly used as a weight loss method, Intermittent Fasting (IF) serves as an alternative approach. The purpose of this study was to investigate how weight influences the acute effect of 4 weeks of IF on stress and hunger levels, sleep quality, and body composition. **Methods**: Sixteen participants with mean age 34.0 ± 11.7 years (8 with body weight ≤80 kg and 8 > 80 kg), completed a four-week session of IF. Participants fasted for 16 hours from the time of their last meal of the evening to the start of their first meal the following day. Participants consumed their normal daily caloric intake within an 8-hour period. Body composition was determined using InBody 770. The Pittsburgh Sleep Quality Index, Cohen Perceived Stress Scale, and a hunger level survey were administered at baseline and post 4 weeks. **Results**: There were no significant differences in mean body fat %, visceral fat, trunk fat, body fat mass, stress, sleep, and hunger level at baseline between subjects with weight ≤ 80 kg and those > 80 kg. Results of the mixed model ANOVA showed that there was a significant reduction in mean body fat%, visceral fat, trunk fat, and hunger level over time ($p=0.017$ ($\eta^2 = 0.35$), $p=0.004$ ($\eta^2 = 0.46$), $p<0.001$ ($\eta^2 = 0.57$), and $p=0.013$ ($\eta^2 = 0.35$), respectively), however, this change did not differ by weight group as determined by p-value for weight x time interaction ($p>0.05$). Results of the paired t- test showed that, among subjects with weight >80 kg, there was a significant reduction in mean body fat %, visceral fat, and trunk fat post 4 weeks versus at baseline (26.6±12.3 versus 27.3±11.8, $p=0.012$ ($d=1.0$); 116.0±78.2 versus 121.3±76.3, $p=0.002$ ($d=1.5$); and, 13.7±7.6 versus 14.4±7.4, $p<0.001$ ($d=2.4$); respectively). However, this change was not as significant in subjects with weight ≤80 kg ($p=0.081$, $p=0.096$, and $p=0.079$, respectively). On the other hand, there was a significant reduction in hunger level among subjects with weight ≤80 kg post 4 weeks versus at baseline (29.1±24.0 versus 60.1±26.3, $p=0.007$ ($d=1.1$)), however, this change was not significant in subjects with weight>80 kg ($p=0.11$).**Conclusion**: Regardless of weight, there were no differences in IF benefits on body fat, visceral and trunk fat. Muscle mass was unchanged. Intermittent Fasting suggests benefits in preserving muscle mass, decreasing body fat and managing hunger levels irrespective of weight. This method is effective for individuals across different weight categories and may be integrated into comprehensive wellness programs. Further research is needed to expand these positive findings.

Disclosures: G. Bains: None. **A. Mohammad:** None. **N. Daher:** None. **E.B. Lohman:** None. **L.S. Berk:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.06/M7

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Effects of sucralose intake on metabolic markers in subjects with overweight or obesity

Authors: *Z. REYES[1], M. RAMOS GARCÍA[5], V. OLVERA HERNÁNDEZ[2], C. GUZMAN[6], M. MARTINEZ LOPEZ[3], J. BLE-CASTILLO[4];
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Abstract: Non-nutritive sweeteners (NSS) have been implemented as substitutes for sugar to reduce caloric intake and prevent body weight (BW) gain. Sucralose stands as the most widely used NNS, yet its health effects have sparked significant controversy over the years. We aimed to examine the effects of sucralose supplementation at realistic doses on metabolic markers in subjects with overweight or obesity. In this randomized, crossover, and controlled trial, 19 subjects with overweight or obesity were allocated to receive daily either sucralose (2 mg/kg/day BW, equivalent to 40% of the acceptable daily intake by FDA) or glucose (control) for 4 weeks and then the alternative intervention. Each treatment was separated by a four-week washout period. A meal tolerance test was performed to evaluate the glycemic and insulinemic responses. In addition, fasting biochemical parameters such as glucose, insulin, cholesterol, triglycerides, HDL-C, and HOMA-IR were measured. All measures were performed before and after the intervention periods. One-way or two-way repeated measures ANOVA was used for data analysis. The consumption of sucralose at the realistic doses used in this study did not significantly impact fasting biochemical markers, nor did it affect glycemic or insulinemic responses in this population. These findings could enhance the body of evidence evaluating the effects of sucralose on subjects with metabolic risk factors.

Disclosures: Z. Reyes: None. **M. Ramos García:** None. **V. Olvera Hernández:** None. **C. Guzman:** None. **M. Martinez Lopez:** None. **J. Ble-castillo:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.07/M8

Topic: F.08. Food and Water Intake and Energy Balance

Support: Shenzhen Science and Technology Research Funding (JCYJ20220818101414032)
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Title: The Effect of Parathyroid Hormone on Mice Brain and Behavior

Authors: *L. ZHANG[1], B. LI[2], N. LIU[3], F. YANG[4];
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Abstract: Objective: The parathyroid hormone (PTH) is an important hormone regulating the calcium homeostasis. Clinical observation indicate that patients of hyperparathyroidism suffer from psychiatric disorders including depression, anxiety and cognitive disorder. Animal studies proved that PTH origin from peripheral system binds to the circumventricular organs in the central nervous system. Yet, the mechanism underlying PTH's influence one the central nervous system remains elusive. **Results:** In this study, we found that intraperitoneal injection of PTH (10 microgram/30g) promotes the total traveling distance on male C57 male mice with or without stress modeling. However, same amount PTH had no significant effect on normal female mice in open-field tests. However, for the female animals undergo ovariectomy (OVX) surgery, PTH inhibits the central time and open arm time in open field tests and elevated plus maze tests. Through 3D behavior analysis, we observed that PTH does not affect the animal behavior categories, but affects the behavioral kinetics in an open field test. The study of the cerebrospinal fluid (CSF) demonstrate that, there is no significant changes to the PTH level in the CSF after PTH injection *i.v*. However, the basal PTH level in female mice are about 100% higher than the male and OVX-female mice. **Conclusion:** This study indicates that the same level of PTH affects animals behavior on different ways for male and female mice. The peripheral administrated PTH does not affect the PTH level in CSF. Therefore, it could be concluded that the PTH induced animal behavorial changes should be mainly conducted through the circumventricular organs.

Disclosures: L. Zhang: None. **B. Li:** None. **N. Liu:** None. **F. Yang:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.08/M9

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: KIST-2E32211

Title: Enhancement of metabolic functions via thermogenic signaling in brown adipocytes using gintonin upcycled Korean red ginseng byproducts for high-fat diet-induced obese mice

Authors: Y. TAMANNA[1], Y. LEE[1], W. KIM[1], S. NAH[2], *H. RHIM[1];
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Abstract: Korean red ginseng (KRG) is widely recognized for its diverse array of phytochemical activities. After the manufacturing process of KRG, residual byproducts are generated. Upcycling these byproducts for pharmaceutical applications holds potential benefits for healthcare and promotes the recycling of bio-resources. Herein, we isolated gintonin, a prominent chemical constituent found in the byproducts of KRG, and investigated its efficacy in improving metabolic function in an obesity-induced high-fat diet (HFD) mouse model. To examine the effect of gintonin extracted from KRG byproducts on HFD-induced obesity, 8-week-old male C57BL/6N mice were used. Mice were separated into four groups (n = 10/group): control (Con), HFD, HFD with a low dose of gintonin (50 mg/kg; HFD+G50), or HFD with a high dose of gintonin (200 mg/kg; HFD+G200) for 16 weeks of oral administration. Additionally, mice were separated into three groups (n = 6/group): control (Con), HFD, and HFD+gintonin, which was administered directly into the third ventricle of the hypothalamus for 14 weeks to confirm its effects on the brain. Evaluations of body weight, food intake, body composition using echo MRI, and activity performance were conducted. Furthermore, energy expenditure, serum biochemical, and histological tissue analysis using H&E and oil red O staining were performed to characterize the metabolic profile. Finally, a qPCR study was conducted to mitigate the thermogenic signaling in brown adipose tissue (BAT). Both oral and hypothalamic consumption of gintonin resulted in reduced body-weight gain without affecting food intake. Gintonin supplementation also led to increased lean mass and enhanced physical performance while decreasing plasma triglyceride and cholesterol levels. Metabolic rate improvements were observed in gintonin-treated groups through thermogenic signaling pathways, especially upregulation of UCP1 in BAT tissue. Moreover, gintonin exhibited effects on lipolysis and inflammation, thereby influencing metabolic health. In conclusion, this work highlights the potential of gintonin upcycled from KRG byproducts in treating HFD-induced obesity and improving metabolism mediated through the thermogenic signaling pathway.

Disclosures: Y. Tamanna: None. **Y. Lee:** None. **W. Kim:** None. **S. Nah:** None. **H. Rhim:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.09/M10

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: DUKE-NUS Scholarship

Title: Dissecting cholesterol metabolism in distinct CNS cell types and the communication between CNS andperipheral systems

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Abstract: Cholesterol provides structural support to cell membranes and serves as a precursor for signalling and essential molecules, such as steroid hormones. Thus, optimal cholesterol level is crucial for life and cholesterol homeostasis is exquisitely regulated. While the central nervous system (CNS) is no exception, there are two points worth of mentioning. One, once the blood-brain barrier (BBB) is formed during embryonic stage, CNS and peripheral cholesterol does not mix. As such, CNS cholesterol has been assumed to regulate autonomously without peripheral input. Second, while dysregulation of cholesterol often associates with neurological and neurodegenerative disorders, whether cholesterol dyshomeostasis *per se* could drive CNS disease remain to be elucidated.We investigate the cholesterol metabolism in distinct CNS cell types, in particular, how cholesterol dyshomeostasis drives neurodegenerative process and impact the CNS and peripheral systems. Our results revealed that varying SREBF-2 levels in specific CNS cell types via cell-type specific deletion and over-expression produce divergent phenotypes in mice, suggesting that there is a cell-type-specific contribution to cholesterol homeostasis in the CNS. Our study focuses on mice with either an overexpression or deletion of SREBP2 in the motor neuron. SREBF2 overexpressing mice exhibited reduced body weights and fat stores, slight motor function deficient and metabolic differences. While mice depleted of cholinergic SREBP2 displayed alopecia or early death between 8-16 weeks of age. These findings suggest a non-cell-autonomous effect of cholinergic cholesterol dysmetabolism both within the CNS and on the peripheral systems.

Disclosures: J. Ho: None. **S. Ling:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.10/M11

Topic: F.06. Autonomic Regulation

Support: NIH Grant 5R01DK130328-03

Title: Neurons in the dorsal vagal complex respond to stimulation of the islet beta cell

Authors: *J. DORNING[1], M. MAKHMUTOVA[2], A. CAICEDO[3];
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Abstract: Vagovagal reflexes have been shown to modulate the physiological functions of various organ systems in the body. The parasympathetic nervous system is known to help regulate the secretion of pancreatic islet hormones in order to maintain glucose homeostasis. However, evidence of a pancreas-specific vagovagal reflex remains elusive. Being the main source of energy for the entire body, blood glucose is a tightly regulated homeostatic parameter.

Dysregulation of glucose control and islet function leads to diabetes, a disease that has reached epidemic levels in the US. We recently determined that vagal sensory neurons innervate the islet, respond to stimulation of the insulin secreting beta cell, and terminate in the nucleus of the solitary tract (NTS). Thus, we hypothesize that vagal sensory neurons communicate the physiological state of beta cells and other islet cells to the central nervous system. We propose that pancreas-innervating vagal sensory fibers project to neurons of the NTS, which then communicate with vagal efferent neurons located in the dorsal motor nucleus of the vagus (DMV). This would establish a pancreas-specific vagovagal circuit that regulates islet function. To begin testing this hypothesis, we selectively stimulated beta cells using a chemogenetic approach in mice and measured neural activity in the dorsal vagal complex with c-Fos immunostaining. We found that beta cell stimulation led to a significant increase (3-fold) in the number of c-Fos positive neurons in the caudal regions of the NTS and the DMV compared to controls. To identify the neuronal phenotype of these beta cell-activated neurons in the NTS, we chemogenetically stimulated beta cells in a transgenic mouse line in which GFP expression is limited to GABAergic neurons (GAD1-EGFP). The number of c-Fos-stained GABAergic neurons in the NTS did not increase compared to controls, suggesting that these inhibitory neurons are not activated by beta cell stimulation. We conclude that non-GABAergic neurons in the caudal NTS and DMV are excited by increased activity of pancreatic beta cells. The concomitant increase in neural activity suggests that the neurons in the NTS responding to beta cell stimulation activate efferent neurons in the DMV, potentially those which innervate the pancreas. We will test this notion by combining local tracing with tracing from the pancreas. We will further establish if these responses in the dorsal vagal complex are directly mediated by the sensory vagus and not by the humoral effects of islet hormones. We expect our studies to define the logic and the neuronal components involved in parasympathetic regulation of islet function.

Disclosures: J. Dorning: None. **M. Makhmutova:** None. **A. Caicedo:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.11/M12

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Inhibition of gut glucose absorption overrides insulin resistance to lower blood glucose levels in obesity

Authors: *H. LIM[1], M.-S. KIM[2];
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Abstract: <META NAME="author" CONTENT="박채범">ObjectiveHypothalamic proopiomelanocortin (POMC)-producing neurons, well-known regulator of energy balance, also modulate glucose metabolism. POMC neuron-specific inhibition of leptin and insulin signaling impairs glucose tolerance and insulin sensitivity, suggesting the importance of metabolic

hormonal signaling in POMC neurons in maintaining glucose homeostasis. We investigated the involvement of the cAMP−protein kinase A (PKA) signaling in POMC neurons in the central regulation of energy and glucose metabolism.MethodsWe generated the mice model with constitutively-activated PKA signaling in POMC-expressing cells (*Prkar1a*$^{\Delta POMC}$ mice) by mating POMC-cre mice and PKA regulatory (inhibitory) subunit *Prkar1a*-floxed mice. We used *Prkar1a*$^{f/f}$ littermates as a wild type control (WT mice). We compared glucose metabolism and gut glucose absorption level between wild and *Prkar1a*$^{\Delta POMC}$ mice.Result*Prkar1a*$^{\Delta POMC}$ mice developed increased fat mass and insulin resistance. This phenotype was related to hypercortisolism by activated PKA signaling in POMC-expressing pituitary corticotrophs as it was significantly reversed by bilateral adrenalectomy. Despite being insulin−resistant, *Prkar1a*$^{\Delta POMC}$ mice had markedly lower blood glucose levels during glucose tolerance test. Enhanced glucose tolerance in *Prkar1a*$^{\Delta POMC}$ mice was largely blunted when glucose was administered intravenously compared to oral administration, suggesting the involvement of gut-mediated mechanisms. We further found the neural circuit that POMC neurons in the arcuate nucleus (ARC) project to the dorsal motor nucleus of vagus (DMV) in the brainstem and then to the jejunum via the vagus nerve. Also, pre-administration of a parasympathetic inhibitor showed attenuated the gut-related phenotype, that indicating these effects are mediated by parasympathetic activation. The molecular mechanism underlying the improved glucose metabolism was that constitutively-activated PKA signaling in hypothalamic POMC neurons inhibited the sodium glucose transporter1(SGLT1) in the upper jejunum brush border of *Prkar1a*$^{\Delta POMC}$ mice. As a result, intestinal glucose absorption was decreased and fecal glucose content was increased in *Prkar1a*$^{\Delta POMC}$ mice. ConclusionWe have found a novel mechanism by which the PKA activation in hypothalamic POMC neurons improves glucose metabolism by inhibiting intestinal glucose absorption. This regulation occurs through the neural circuit of ARC-DMV-vagus-gut.

Disclosures: H. Lim: None. **M. Kim:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.12/M13

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH IRACDA 1K12GM093854
NIH R01DK103676

Title: A sex-dependent action of irisin on ventromedial hypothalamus (VMH) glucose-inhibited (GI) neurons: implications for sex differences in glucose usage during exercise

Authors: *G. VAIL[1], V. H. ROUTH[2];
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Abstract: Regulation of energy usage is a tightly controlled homeostatic function that sometimes differs depending on sex. For example, submaximal endurance exercise stimulates lipid oxidation more so in females than in males, where glucose utilization is initially dominant. The brain drives this sex difference, potentially through glucose inhibited (GI) neurons in the ventromedial hypothalamus (VMH). VMH-GI neurons increase activity as glucose decreases to restore glucose levels via sympathetic activation of hepatic gluconeogenesis. Using mouse brain slice patch-clamp techniques, we exposed VMH-GI neurons to irisin, a myokine released by muscle during exercise. We hypothesized that irisin, acting as a signal of exercise, modulates VMH-GI activity in a sex-dependent manner. Consistent with this, irisin had no effect on VMH-GI neurons in males. However, in females irisin blunted the typical depolarization and increased cellular resistance of VMH-GI neurons seen in response to a glucose decrease from 2.5 to 0.1 mM. The effect of irisin was only significant during low-estrogen estrus cycle stages, suggesting a competitive interaction with estrogen. Western blot analysis revealed that irisin abolished the typical increased phosphorylation of the cellular fuel sensor AMP-activated protein kinase (AMPK) by lowered glucose in females, but not males. Lastly, exposure to brain-derived neurotrophic factor (BDNF) mimicked the sex-dependent effects of irisin; however, the effect of BDNF did not vary with estrus cycle stage. These data suggest a role for irisin in mediating sex differences in glucose utilization during exercise, and indicate estrogen, AMPK, and BDNF as potential mechanistic factors. Understanding how sex and hormones influence exercise will allow for more personalized approaches to nutritional and exercise strategies, which are especially important for diabetic and pre-diabetic patients.

Disclosures: G. Vail: None. **V.H. Routh:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.13/M14

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Schweizerischer Nationalfonds (SNF) postdoc mobility grant

Title: Exercise modulates diet via the gut-brain axis

Authors: *L. BOCCIA, J. BETLEY;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: The escalating global health crisis caused by increases in obesity and consumption of sugar-laden foods requires a re-exploration of effective countermeasures. Given the pleotropic benefits of exercise on health, obesity and diabetes, our research explored how exercise training influences health. Based on prior reports demonstrating dietary preference changes in humans on exercise regimens, We explored the possibility that changes in dietary preferences during exercise are hard wired and potentially encoded by mechanisms that can be harnessed to yield

effective obesity and diabetes treatments. We first determined that long term exercise training (>6 weeks) in rodents reduces their consumption of diets enriched in sucrose. We find that these changes are not encoded by a change in the hedonic value of sugar taste, but rather through alterations in gut to brain signals that reduce the value of ingested sugar. We are currently exploring the role of the gut microbiome, microbiome derived metabolites, and incretin signaling in mechanistically coding for these dietary changes. These findings not only deepen our understanding of the gut-brain axis but also open avenues for developing novel strategies to combat dietary-related health issues.

Disclosures: L. boccia: None. **J. Betley:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.14/M15

Topic: F.08. Food and Water Intake and Energy Balance

Support: Grant CONAHCYT-1243407 to: MSRG
Grant: CNRG-INIFAP-2024
Grant: División de Ciencias Biomédicas-CUAltos- UdeG
Grant: Doctorado en Biociencias-CUAltos-UdeG

Title: The interaction of the gut-brain axis in obesity in male Wistar rats on a high-calorie diet and the effect of apple cider vinegar on the intestinal microbiota.

Authors: *M. REVELES GONZÁLEZ[1], G. CAMARGO HERNÁNDEZ[3], L. A. RAMIREZ CONTRERAS[2], R. ARTEAGA GARIBAY[4], S. SANCHEZ ENRÍQUEZ[1];
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Abstract: Obesity is a chronic and multifactorial disease, a public health problem worldwide, highlighting the importance of the interaction between the intestine and the brain in the regulation of body weight and metabolism, known as the gut-brain axis. Therefore, obesity is related to intestinal dysbiosis, an imbalance in the composition and function of the intestinal microbiota. Furthermore, intestinal dysbiosis is associated with various conditions such as metabolic diseases, neuromusculoskeletal conditions, endocrine pathologies, neurodegenerative and cardiovascular diseases. In obesity there are communication mechanisms of the gut-brain axis, so the gastrointestinal system not only digests and absorbs nutrients, but also acts as an endocrine organ that houses a diverse community of microorganisms called intestinal microbiota. This microbiota, along with hormonal and neuronal signals, influences the regulation of appetite, satiety, and fat storage. Studies have shown that obese people show an altered response to satiety

cues, resulting in excessive food intake. Methods: It has been observed in our study groups in n=20 adult male Wistar rats divided into 5 groups: healthy control, control; experimental; conventional and combined, the last four, fed with a diet rich in saturated fats at 14.28% and 46.58% carbohydrates, values determined with a bromatological study, this for the energy increase of the food resulting in a greater preference in these groups of animals for foods high in fat and sugar, suggesting dysfunction in food-related brain reward circuits. In the healthy control group fed with a standard diet, they had no alterations in their diet and in terms of the body weight of the animals, through the ANOVA statistical analysis, they had significant differences with a value of $p = <0.05$ and $p = 0.001$ compared to the others. groups with excessive weight. And in relation to the mean abdominal perimeter (MAP) it was significant with a $p= 0.042$ between the experimental group $\bar{X} \pm SD$ of 20.4 ± 1.11 against the healthy control group $\bar{X} \pm SD$ of 17.3 ± 1.7. Preliminary conclusions: Apple cider vinegar will be used to control blood glucose and lipid levels, so a modulation of the intestinal microbiota is expected and therefore an improvement in the gut-brain axis.

Disclosures: M. Reveles González: None. **G. Camargo Hernández:** None. **L.A. Ramirez Contreras:** None. **R. Arteaga Garibay:** None. **S. Sanchez Enríquez:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.15/M16

Topic: F.08. Food and Water Intake and Energy Balance

Support: Science Foundation Ireland (Grant No. SFI/12/RC/2273_P2).
Irish Research Council GOIPG/2021/942
Saks Kavanaugh Foundation

Title: Modulation of murine hippocampal synaptic plasticity by microbial metabolites: sex-specific effects of the short-chain fatty acid butyrate

Authors: M. K. COLLINS[1], C. ROSELL CARDONA[2], G. CLARKE[3], ***K. J. O'RIORDAN**[2], J. CRYAN[4];
[1]Anat. and Neurosci., Univ. Col. Cork, Cork, Ireland; [2]APC Microbiome Ireland, Univ. Col. Cork, Cork, Ireland; [3]Psychiatry, Univ. Col. Cork, Cork, Ireland; [4]Vice President for Res. & Innovation, Univ. Col. Cork, Cork, Ireland

Abstract: The gut-brain-axis is a system of bidirectional communication between the gastrointestinal tract and the brain. This communication has profound influence on human health and disease and in everyday physiological processes such as cognition. Microbial metabolites such as short-chain fatty acids (SCFAs) produced mainly through the fermentation of dietary fibre, are one of the key mediators of this communication network. Previously, we observed that germ-free mice display a sex-dependent impairment in synaptic plasticity. Here, we examined

the effects of the three most abundantly produced SCFAs in the gut, acetate, butyrate, and propionate, on *ex vivo* hippocampal slices at physiologically relevant concentrations, to explore potential sex-specific mechanisms underlying their action. A 40-minute exposure to 3μM butyrate enhances Schaffer collateral long-term potentiation (LTP) in both male and female mice. Our hypothesis followed that the observed effect may occur through butyrate's activation of the G protein-coupled receptor, free fatty acid receptor 3 (FFAR3). While butyrate also acts as a HDAC inhibitor, it does so in the mM range, leaving HDAC inhibition as an unlikely mechanism of action here. FFARs including FFAR3 are present in the human and mouse hippocampus. Butyrate preferentially activates FFAR3 over other similar receptors present such as FFAR2. Therefore, we investigated the involvement of this receptor using the FFAR3 antagonist and HDAC inhibitor, β-hydroxybutyrate (BHB). FFAR3 inhibition abolishes the enhanced potentiating effect of butyrate on LTP in female slices while leaving its efficacy intact in slices from male counterparts. Notably, BHB alone did not affect LTP in either sex, suggesting differential regulation of SCFA signalling pathways in the hippocampus between the sexes. The conservation of enhanced LTP in males may point to differential expression of FFAR3 between the sexes. To elucidate potential sources of this dimorphism we examined mRNA expression levels of FFARs and SCFA transporters in CA1 hippocampal tissue from male and female animals. Moreover, we have explored the potential for other SCFAs to have similar effects on hippocampal plasticity. Data suggests a lack of discernible influence of propionate over LTP, indicating a specific role for butyrate in modulating hippocampal synaptic plasticity at these concentrations. Further, propionate shows a possible effect over basic synaptic efficacy. Ongoing studies are focused on the role of the SCFAs over short-term plasticity or basic synaptic efficacy. This work highlights the potential for gut microbiota to shape brain function.

Disclosures: M.K. Collins: None. **C. Rosell Cardona:** None. **G. Clarke:** Other; G.C. received honoraria from Janssen, Probi, and Apsen and research funding from Pharmavite and Fonterra and is a paid consultant for Yakult and Zentiva.. **K.J. O'Riordan:** None. **J. Cryan:** Other; J.F.C. has spoken at conferences organized by Mead Johnson, Ordesa, and Yakult and has received research funding from Reckitt, Nutricia, Dupont/IFF, and Nestle..

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.16/M17

Topic: F.08. Food and Water Intake and Energy Balance

Support: SFI grant no. 12/RC/2273_P2
ISIC Grant no. 895999

Title: Habitual Coffee Intake Shapes the Gut Microbiome and Modifies Host Physiology and Cognition

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Abstract: Coffee consumption affects physiology, the gastrointestinal system, stress, cognition, and the gut microbiome. Due to the complex composition of the beverage, the mechanisms behind these effects remain poorly understood. To assess what degree the effects of coffee are mediated by the microbiota-gut-brain axis - the bidirectional communication between the gut microbiome and the brain - and whether such changes occur independent of caffeine. We recruited healthy participants that did (N = 31) or did not (N = 31) habitually drink coffee. After assessing baseline differences in physiology, cognition, and microbiome, we performed an intervention with the coffee drinking group. After a 2-week washout period, participants were randomly assigned to either receive caffeinated or decaffeinated coffee for three weeks. We performed faecal and urinary metabolomics including targeted coffee metabolites, faecal metagenomics, measured cytokines, and collected physiological and psychological questionnaires at baseline, post-washout, and post-reintroduction of coffee. Additionally, we assessed faecal microbiome at two, four- and fourteen-days post withdrawal and reintroduction to investigate acute changes in the microbiome. We found differences in coffee drinkers versus non-coffee drinkers at baseline in terms of faecal microbiome and metabolome, as well as in inflammatory cytokines and psychological questionnaires. Several of these differences, most notably in the faecal metabolome, could be reversed in a coffee washout state. We also observed acute changes in the microbiome post-reintroduction of coffee, with many factors altered independent of caffeine. Interestingly, we also found a relationship between strains altered by coffee consumption, the metabolites they produce and cognitive outcomes in several questionnaires related to memory, impulsivity, and emotional reactivity. Together, these data unmask novel effects of coffee intake on microbiota-gut-brain axis signaling that may exert positive effects on physiology, behavior and that the microbiome may represent a biomarker of habitual coffee consumption.

Disclosures: G.M. Moloney: None. **S. Boscaini:** None. **T.F.S. Bastiaanssen:** None. **C. O' Leary:** None. **A. Ferri:** None. **E. Schneider:** None. **A. Chinna Meyyappan:** None. **K. Berding:** None. **D. Del Rio:** None. **P. Mena:** None. **L. Bresciani:** None. **L. Zeraik:** None. **C. Long-Smith:** None. **C. Carbia:** None. **K.J. O'Riordan:** None. **G. Clarke:** None. **J.F. Cryan:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.17/M18

Topic: F.08. Food and Water Intake and Energy Balance

Support: European Union's Horizon 2020 research and innovation programme under grant agreement No. 862568 (www.sprint-h2020.eu)

Title: The Pesticide Glyphosate Induces Sex-Dependent Behavioural Changes in Mice: A Role for the Gut Microbiota

Authors: *R. MATSUZAKI[1,2], S. CAGUN[1,2], P. FITZGERALD[1], B. VALDERRAMA[1,2], T. BASTIAANSSEN[3], E. GUNNIGLE[2], J. CRYAN[1,2];
[1]Univ. Col. Cork, Cork, Ireland; [2]APC Microbiome Ireland, Cork, Ireland; [3]Dept. of Psychiatry, Amsterdam UMC, The Netherlands, Amsterdam, Netherlands

Abstract: The gut microbiota plays a critical role in maintaining the physical and mental well-being of the host. It is influenced by various factors, including xenobiotics like pesticides. Glyphosate, a globally used herbicide, is considered to be harmless to humans as it targets the shikimate pathway, which is absent in animal cells. However, this idea is now being challenged as research suggests that glyphosate may negatively affect the pathway in microorganisms residing in the gut, such as gut bacteria, which could have an impact on the host. Previous research in animals has tested either high dose exposure for toxicological effects or commercially available glyphosate-based herbicides. Contrary to expectations, the understanding on impact of glyphosate exposure at doses relevant to human health indicators, such as Acceptable Daily Intake (ADI), is currently lacking. In this study, male and female adult C57BL/6 mice were exposed to glyphosate (0, 0.5[ADI in Europe]), 5, 50 mg/kg/day) via drinking water chronically. Behaviours were assessed for anxiety, stress-coping, cognition and sociability. Caecal microbiota transplant (CMT) was conducted to examine the involvement of the gut microbiota, by transferring caecal content of glyphosate-exposed mice to glyphosate-naïve mice. Interestingly, glyphosate exposure in males increased anxiety in the open field test and diminished social novelty preference in the three-chamber test. In contrast, glyphosate exposure in females had limited alterations in behaviours with the only change recorded being a reduction in locomotion in the open-field test. Interestingly, the social behavioural phenotype in males was transferred by CMT suggesting the microbiota being the underlying drive for this behavioural impairment. Further analysis is warranted to understand better the potential mechanisms underlying these behavioural impairments. To achieve this, we aim to analyse compositional and functional changes in the gut microbiome upon glyphosate exposure. Additionally, changes in the gut and brain will be explored with a focus on neuroplasticity and physiology.

Disclosures: R. Matsuzaki: None. **S. Cagun:** None. **P. Fitzgerald:** None. **B. Valderrama:** None. **T. Bastiaanssen:** None. **E. Gunnigle:** None. **J. Cryan:** None.

Poster

PSTR474: Metabolic Syndrome, Microbiome, and Integration of Peripheral Signals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR474.18/M19

Topic: F.06. Autonomic Regulation

Support: Huck Institute of the Life Sciences
Department of Biobehavioral Health at Penn State
Biotechnology and Biological Sciences Research Council
BB/R021317/1

Title: An Analysis of the Relationship between the Gut Microbiome and Temperament

Authors: *B. HATI[1], D. KADIDAHL[2], E. K. MCMAHON[4], S. A. CAVIGELLI[3];
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Abstract: Temperament is important for survival and overall health across many species. Yet despite the advances in understanding and characterizing temperament, the underlying interplay of physiological mechanisms that drive the emergence and characteristics of a temperament profile remain ambiguous.Behavioral, physiological and health implications of gut microbiome is still a relatively new area of research, but several interesting findings suggest that the gut microbiome is important in behavioral phenotypes. The gut microbiome is a part of the gut-brain axis which induces various effects through a bidirectional communication network between the enteric and central nervous system that leverages bacterial metabolites, local neurotransmitters and the hypothalamic-pituitary-adrenal (HPA) axis as methods of communication. Certain gut microbiota have been found to reduce anxiety-like behavior and depression, suggesting innate underlying relationships between the gut microbiome and behavior. The recent emergence of the influential role of the gut microbiome suggests that it may be involved in the interplay of physiological metrics that influence temperament.The objective of this observational study was to investigate whether temperament and/or related physiological processes were related to the gut microbiome in a sample of 49 individually housed outbred adult male Sprague Dawley rats. Temperament was estimated from behavioral responses to different test arenas at multiple time points and then compared to alpha diversity metrics, relative abundance of bacteria, and glucocorticoid and serotonin receptor/transporter expression in the right ventral hippocampus. The study first profiled the overarching microbial composition of the rats before investigating the relationships between the microbiota and brain gene expression and behavior, identifying associations between certain temperaments and abundance of microbiota. Our results indicate that gut microbiota diversity and relative abundance of certain phyla relate to certain stable temperament profiles through glucocorticoid expression.

Disclosures: B. Hati: None. **D. Kadidahl:** None. **E.K. McMahon:** None. **S.A. Cavigelli:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.01/M20

Topic: G.09. Drugs of Abuse and Addiction

Support: JSPS KAKENHI 22K06431
JSPS KAKENHI 17K07110

Title: Crosstalk between AQP4-dependent ATP/adenosine release and dopamine neurotransmission in cocaine-induced depressive behavior

Authors: *M. MORITA;
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Abstract: We have reported AQP4-dependent ATP release and following accumulation of extracellular adenosine in hypoosmotically-treated hippocampal slices by using a biosensor, which is a cell line equipped with a gene set for adenosine-induced $[Ca^{2+}]i$ increase (Yamashiro et al, J Neurochem 2017). Since the crosstalk between adenosine and dopamine is well established, especially the dimerization of their receptors in the striatum, the involvement of AQP4-depenent adenosine release in the pathological changes of dopamine neurotransmission during the depressive behavior following cocaine withdrawal was investigated. The depressive behavior was suppressed in AQP4 ko mice as well as by acute treatment of adenosine A1 receptor antagonists, suggesting the involvement of AQP4-dependent adenosine release in depressive behavior. In the striatum, cocaine increased adenosine release and enhanced presynaptic inhibition of dopamine release via A1 receptor. Since the reduced dopamine release by cocaine was occluded in AQP4 ko mice, cocaine most likely increased AQP4-dependent adenosine release and caused depressive behavior by increasing presynaptic inhibition of dopamine neurotransmission. In contrast, cocaine influenced dopamine system by inactivating A1 receptor in medial prefrontal cortex (mPFC). Cocaine did not affect adenosine release in mPFC, but occluded the inhibitory effect of A1 antagonist to dopamine release. Since antagonists for GABAA receptor or group II metabotropic glutamate receptor (mGluRII) also occluded the inhibitory effect of A1 antagonist to dopamine release, A1 receptor was supposed to presynaptically suppress the glutamate release causing presynaptic inhibition of GABA release via mGluRII and upregulates GABAergic inhibition of dopamine release. The inhibitory effect of A1 antagonist was occluded by cocaine and in AQP4 ko mice, but maintained in cocaine-treated AQP4 ko mice in consistent with the occlusion of cocaine-induced depressive behavior in AQP4 ko mice. Thus, cocaine is most likely inactivates A1 receptor through AQP4-dependent adenosine release. Since AQP4 is selectively expressed in astrocytes, our results propose that cocaine withdrawal causes depressive behavior by influencing astrocytic ATP/adenosine release, presumably through neuroinflammation and reactive activations of astrocytes.

Disclosures: M. Morita: None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.02/M22

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA-IRP

Title: Investigate the role of ENT4 in controlling adenosine and dopamine levels in mouse striatum

Authors: *W. SANCHEZ[1], Y. CHANG[2,3], C. R. QUIROZ[1], W. P. REA[1], Y. CHERN[2], S. FERRE[1];
[1]Natl. Inst. on Drug Abuse, NIH, Baltimore, MD; [2]Inst. of Biomed. Sci., Academia Sinica, Taipei, Taiwan; [3]National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD

Abstract: Dopamine plays pivotal roles in drug addiction development. The intricate interplay between dopamine and adenosine receptors, such as the formation of D_1R-$A_{2A}R$ and D_2R-A_1R hetero-tetramers, profoundly influences their downstream signaling pathways, and thus offering a new therapeutic avenue for Substance Use Disorder (SUD). Equilibrative Nucleoside Transporter Type 4 (ENT4) displays heightened expression in several inhibitory neurons and has been demonstrated a preference for dopamine transport over adenosine in-vitro. Despite its critical role in regulating extracellular adenosine and dopamine, the neuronal and in vivo functions of ENT4 remain unexplored. In the present study, we employed the ENT4 inhibitor, TC-T6000, to assess ENT4's role in modulating extracellular adenosine and dopamine levels in the dorsal striatum, a primary site for rewarding behavior and addiction development. Using locomotor activity as a functional readout, we observed a significant reduction in locomotor activity in non-reserpinized mice but not in reserpine-treated mice after TC-T6000 treatment. This finding demonstrates for the first time that ENT4 has a behavioral regulatory role in-vivo. Furthermore, considering that ENT4's action requires an acidic environment, it also suggests that ENT4 function necessitates neurotransmitter release and proton transmission in-vivo. To further elucidate whether inhibition of ENT4 induces adenosine-mediated locomotor reduction, we employed the fluorescent adenosine biosensor ($GRAB_{ADO}$) with fiber photometry and successfully demonstrated an increase in extracellular adenosine levels following ENT4 inhibitor administration. Taken together, our preliminary results indicate decreased locomotor activity due to elevated adenosine levels following ENT4 inhibition in mice. Given ENT4's demonstrated preference for transporting dopamine over adenosine in vitro, future investigations will involve assessing dopamine levels via microdialysis and fiber photometry. Additionally, we will explore the crosstalk between adenosine and dopamine receptors. This study will enhance our understanding of ENT4 and evaluate its potential as a new therapeutic target for drug addiction. This work was supported by NIDA/NIH.

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Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.03/M23

Topic: G.09. Drugs of Abuse and Addiction

Title: Optogenetic activation of RhoA in dopamine D2 receptor-expressing neurons in the nucleus accumbens core inhibits the development of cocaine-induced conditioned place preference

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Abstract: Environmental cues associated with drug use are known to frequently trigger relapses, indicating that conditioned contexts and cues are crucial in the expression of addictive behaviors. RhoA, a well-known GTPase, has a regulatory role in morphological neuroplasticity and accompanied signaling pathways. Further, it is known to be importantly involved in drug addiction. In this study, the effects of optogenetic modulation of RhoA in dopamine (DA) D2 expressing neurons in the nucleus accumbens (NAc) on the development of Conditioned Place Preference (CPP) are investigated. During the acquisition phase of the CPP process, paired group received cocaine (20 mg/kg) with or without bilateral optical stimulation (470 nm) by the pre-implanted microscale inorganic light-emitting diodes (μ-ILED) probes to the NAc in one chamber, while received saline only in another chamber. This process repeated three times. A separate control group received saline in both two chambers. Two days following the completion of the acquisition phase, all rats underwent a preference assessment for the chambers with no injection and stimulation. Interestingly, paired group with optical stimulation showed significantly reduced preference toward the chamber previously associated with cocaine, whereas increased preference toward the chamber associated with cocaine was saved without optical stimulation. These results suggest that a selective RhoA activation, particularly in DA D2-expressing neurons within the NAc, may play an important role as a molecular switch in mediating the conditioning effects of cocaine.

Disclosures: J. Park: None. **D. Han:** None. **M. Kwak:** None. **J. Jeong:** None. **W. Kim:** None. **J. Kim:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.04/M24

Topic: G.09. Drugs of Abuse and Addiction

Title: Striatal cAMP response to in-vivo dopamine modulation

Authors: *J. LEE[1], A. SHERIDAN[2], H. L. PUHL III[3], A. HOLDER[4], S. M. AUGUSTIN[5], D. LOVINGER[2];
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Abstract: Dopamine serves as a critical neuromodulator within the striatum, influencing circuit physiology and animal behaviors associated with reward-related events. Its release and subsequent intracellular signaling play pivotal roles in regulating reinforcement learning and drug addiction. However, distinct subregions within the striatum, such as the dorsal and ventral segments, are characterized by unique molecular, cellular, and behavioral properties. Consequently, the extent to which different striatal circuits distinctly modulate signal transduction, such as via cAMP, remains largely unexplored. In this study, we employed a novel cAMP biosensor to delineate differential cAMP modulation in the Nucleus Accumbens (NAc) and Dorsolateral Striatum (DLS) alongside dopamine modulation. Initially, we administered intraperitoneal injections of cocaine (15mg/kg) in mice to induce alterations in dopamine levels while inhibiting dopamine reuptake. Utilizing a genetically encoded dopamine indicator (dLight 1.3), we observed a gradual increase in baseline fluorescence signals, indicative of average dopamine release, within both the NAc and DLS post-cocaine injection. Consistently, we observed progressive increases in cAMP levels within both the NAc and DLS through our cAMP biosensor. Further experiments aimed to induce time-specific, phasic dopamine release using Pavlovian conditioning. In the NAc, we noted a slow modulation (20-30 sec) of cAMP levels within dopamine D1 receptor-expressing medium spiny neurons (D1-MSNs), coinciding with the onset of high-tone sound cues (CS+). This modulation pattern resembled that of PKA activity measured by PKA biosensors (t-AKAR-alpha). Conversely, within the DLS, we did not detect similar slow modulation during the presentation of CS+ or upon reward delivery. To elucidate the region-specific interplay between dopamine release and cAMP modulation, ongoing investigations involve optically evoked cAMP measurements.

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Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.05/M25

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant RO1DA047785
NIH Grant RO1DA056720

Title: Exploring the role of the autophagy protein Becn2 signaling pathway in dopamine-regulated cocaine reward

Authors: *A. SALAZAR[1], D. YANG[3], Q. KONG[2], C. HE[3], M. XU[2];
[2]Dept. of Anesthesia and Critical Care, [1]Univ. of Chicago, Chicago, IL; [3]Cell and Developmental Biol., Northwestern Univ., Chicago, IL

Abstract: Autophagy is a key cellular process involving the breakdown and recycling of cellular components through lysosomal degradation. It is governed by over 30 autophagy-specific genes and operates both selectively, targeting specific cellular cargo, and non-selectively. Although autophagy's malfunction is associated with numerous diseases such as cancer and neurodegeneration, its role in neurotransmission and substance use behaviors remains largely unexplored. Cocaine use disorder, a widely used illicit drug, poses a significant public health challenge with increasing overdose fatalities, a high propensity for relapse, and currently no FDA-approved medications to address this chronic brain disease. Our prior studies have identified Beclin 2 (Becn2) as a novel regulator of cocaine reward behaviors by modulating dopamine signaling and the levels of presynaptic D2 receptors (D2Rs) in dopamine-producing neurons of the ventral tegmental area (VTA). Dopamine receptors, particularly D2Rs, are critical G protein-coupled receptors that influence the neurobiological effects of cocaine. Increasing and decreasing D2R expression has been found to alter cocaine intake and behavioral responses, with low D2R availability in the brain being correlated to heightened drug-seeking activity. Despite this, the mechanisms controlling D2R expression are not fully elucidated. Given that D2Rs are present in both presynaptic dopaminergic neurons and postsynaptic D2 receptor-positive medium spiny neurons (D2-MSNs), our current research explores the regulation of postsynaptic D2Rs in D2-MSNs by Becn2 using a cell-specific knockout model. Utilizing this model, we are conducting intravenous cocaine self-administration (IVSA) studies to examine drug acquisition, dose-response relationships, drug extinction, and reinstatement. Our initial IVSA experiments with both wild type and Becn2 knockout mice have provided foundational insights. To strengthen these findings, additional rounds of IVSA experiments are planned to increase our subject numbers and enhance the robustness of our statistical analysis. These experiments aim to further establish the importance of Becn2 in mediating cocaine reward behaviors and may potentially provide new therapeutic targets for treating cocaine use disorder.

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Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.06/M26

Topic: G.09. Drugs of Abuse and Addiction

Support: F31-DA057830-01A1
R00DA045795
P30DA033934
R01DA058958

Title: Re-engineered transcription factors reveal's role of ZFP189 in cocaine use disorder (CUD)

Authors: *J. A. PICONE[1], A. HASSAN[2], R. K. KIM[3], G. SILVA[4], N. L. TRUBY[5], P. J. HAMILTON[6];
[1]Anat. and Neurobio., Virginia Commonwealth Univ. Neurosci. Grad. Program, Richmond, VA; [2]Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA; [3]Neurosci. Grad. Program, Virginia Commonwealth Univ., Richmond, VA; [4]Virginia Commonwealth Univ., Richmond, VA; [5]Anat. and Neurobio., Virginia Commonwealth Univ., RICHMOND, VA; [6]Neurosci., Virginia Commonwealth Univ., Richmond, VA

Abstract: Reprogramming transcription factor function regulates cocaine specific transcriptional and behavioral responses Authors*J.A. Picone, K. Kim, D.P. Lira, G.M. Silva, N.L. Truby, X. Cui, P.J. Hamilton; Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine., Richmond, VA**DisclosureJ.A. Picone:** None. K. Kim: None. D.P. Lira: None. G.M. Silva: None. N.L. Truby: None. X. Cui: None. P.J. Hamilton: None**Abstract**Understanding the molecular substrates of the stages of drug addiction may allow for the design of pharmacotherapies that block or reverse key events of the progression of drug addiction. *Zfp189* is a CREB-target gene which itself encodes an unstudied nucleus accumbens (NAc) neuronal transcription factor that has been demonstrated to regulate transcriptional adaptations following drug- or stress-experience. Published data reveals that using the CRISPR/dCas9-mediated CREB delivery to the *Zfp189* CRE site increases *Zfp189* mRNA levels in the NAc and decreases reward associations for mild doses of cocaine. To further examine the downstream relationship between ZFP189 and physiological response to saline, cocaine, and morphine, three reprogrammed synthetic ZFP189 transcription factors were used to study drug-induced behavior and transcription. Three ZFP189 variants used were: $ZFP189^{WT}$, $ZFP189^{NFD}$, and $ZFP189^{VPR}$. Mice received one of these ZFP variants to the NAc via viral-mediated gene transfer. We then performed a drug locomotor sensitization assay with saline, cocaine, or morphine. In response to cocaine treatment, mice with $ZFP189^{VPR}$ intra-NAc moved significantly more than the $ZFP189^{WT}$ group. More interestingly, this increased locomotion is unique to cocaine experience, as there is no difference in locomotor activity between the ZFP189 variant groups in response to saline or morphine administration. We performed cocaine intravenous administration and observed significant changes in rates of cocaine seeking behaviors between the ZFP189 TFs, immediately following surgery and after a period of forced abstinence. RNA sequencing of manipulated NAc tissues from these mice revealed that the differences in behavioral response to cocaine across the variant groups coincided with transcriptional changes. Specifically, $ZFP189^{VPR}$ was only able to regulate NAc transcription in mice that had been treated with cocaine. These results suggest ZFP189 specifically drives cocaine-induced transcription and behaviors.

Disclosures: J.A. Picone: None. **A. Hassan:** None. **R.K. Kim:** None. **G. Silva:** None. **N.L. Truby:** None. **P.J. Hamilton:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.07/M27

Topic: G.09. Drugs of Abuse and Addiction

Support: RS3684

Title: Unravelling the role of dopamine and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32) in addiction.

Authors: *M. R. GREENER;
Univ. of Nottingham, Nottingham, United Kingdom

Abstract: We are amidst a global addiction crisis, yet stigmas surrounding substance use disorders (SUDs) counterintuitively prevail. Understanding and appreciating the neurobiology of addiction is essential to dissolving this stigma, and for the development of new pharmacological agents to improve upon currently narrow therapeutic options. Dopamine- and cAMP-regulated phosphoprotein , Mr 32 kDa (DARPP-32) is critical to the pathogenesis of addiction. Through site-specific phosphorylation, namely Threonine-34 and Threonine-75, DARPP-32 acts as either a protein phosphatase-1 (PP-1) or protein kinase A (PKA) inhibitor which leads to modulation of numerous addictive signalling cascades. Compounds capable of altering DARPP-32 signalling in this way could prevent or reverse SUDs. The aim of this project is to further define the role of DARPP-32 in the processing of drugs of abuse and support robust investigations into compounds that could pharmacologically modulate it. Through a combination of transcriptomics, molecular biology and phospho-proteomics, we have elucidated interactions between DARPP-32 and the following substances of abuse; ethanol (an alcohol); cocaine (a psychostimulant); THC (a cannabinoid); morphine (an opioid), and psilocin (a psychedelic). The results from these experiments have provided novel insight into the signalling of DARPP-32 and its downstream signalling partners in the presence of drugs of abuse. They provide additional weighting to the significance of DARPP-32 in the pathophysiology of SUDs through a complete analysis of DARPP-32 from the transcript to post-translational modifications stage.

Disclosures: M.R. Greener: None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.08/

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSERCDG 315827

Title: Long-term impacts of bupropion exposure during critical developmental periods on reward learning

Authors: *S. N. SMITH, M. R. HOLAHAN;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Throughout post-natal development, the brain's reward system undergoes critical changes for the establishment and maturation of connections that underlie the emergence of adaptive behaviours. This can be disrupted by psychoactive drugs which alter patterns of connectivity and neurotransmission, resulting in maladaptive behavioural output. Bupropion (BUP) is a dopamine and norepinephrine reuptake inhibitor used off-label to treat ADHD in children and adolescents. The current study examined the short- (on drug) and long- (off drug) term impacts of BUP during critical developmental periods. Male and female Long-Evans rats (n=42) were administered 10 or 20 mg/kg BUP or saline (s.c.) for one week during either preadolescence (p18-24) or peri-adolescence (p34-40). On the second injection day, both BUP doses elicited increased locomotion in peri-adolescent but not preadolescent rats. On the last injection day, both BUP doses elicited a significant increase in locomotion in preadolescent rats, with a more pronounced effect in peri-adolescent rats. Seventeen days later, operant training and extinction, progressive ratio and locomotor tests were conducted. No significant long-term effects on locomotion were observed. During extinction and progressive ratio tests, peri-adolescent rats in the high-dose condition exhibited a significant increase in inactive lever pressing over time. No significant differences were found in the preadolescent group. In summary, on-drug effects of BUP seem to be greater during peri-adolescence given the observed hyperactivity at both doses. Exposure to BUP during peri-adolescence also had long-term effects evidenced by reduced stimulus discrimination when reward delivery was inconsistent.

Disclosures: S.N. Smith: None. **M.R. Holahan:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.09/M28

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Start-up funds

Title: The effects of cannabinoids on progressive-ratio responding for sucrose

Authors: *N. SWALVE, J. GRAY, C. S. DANIELS, C. EARL;
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Abstract: Many states and nations are beginning to legalize marijuana for both medical and recreational purposes yet it is still unlawful at the federal level. Due to marijuana's federal status, little is known regarding both the short- and long-term consequences of cannabinoids, the psychoactive compounds in marijuana that produce its effects. Furthermore, not much is known about how individual and combined administration of cannabinoids affect feeding-related motivation. The effects of cannabinoids, both alone and in combination, on feeding motivation was investigated in this study. During the initial training sessions, rats were trained to lever press for sucrose. Injections were given in four separate groups: WIN55,212-2, CBD alone, a combination of WIN and CBD, and saline. They were then tested on a progressive ratio schedule, where the schedule increased daily until rats reached their breaking point, the point at which rats no longer worked for the reinforcer (e.g. 32 lever presses for one reinforcer or 256 lever presses for a single reinforcer). We compared the breakpoints and response levels among the groups to see if the different types of cannabinoids affected the motivation to respond to a food reinforcer, finding differences between groups in lever-pressing and breakpoints. This suggests that cannabinoids play differing roles on motivation for sucrose.

Disclosures: N. Swalve: None. **J. Gray:** None. **C.S. Daniels:** None. **C. Earl:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.10/M29

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R15 DA016285-05
State of Washington

Title: Chronic CBD effects on sucrose self-administration by adult male and female Long-Evans Rats

Authors: *J. GRIMM, C. BACON, K. SANKO, L. JACKSON-LINVEL, E. VAN DEN DUNGEN, A. O'SHEA, B. OLIVER, T. TRICKETT;
Western Washington Univ., Bellingham, WA

Abstract: Cannabidiol (CBD) is now readily available globally. Ingested, inhaled, and transdermal self-administered, CBD is used for a growing list of indications including chronic pain, anxiety, and depression. Unlike tetrahydrocannabinol (THC), CBD is not known to produce psychoactive effects and is currently not indicated to have an abuse potential. However, given the widespread adoption of CBD, including its use in combination with sweetened beverages and consumables (e.g., gummies), it is of interest to know if CBD has effects on food-directed behaviors. In a small n preliminary study, we found that a single 20 mg/kg intraperitoneal (IP) injection of CBD tended to increase responding for 10% sucrose by adult female, but not male, rats two days after injection. In the present pilot study, rats were instead pretreated with 20

mg/kg IP CBD daily for a total of seven sessions followed by seven sessions with no drug pretreatment. Rats responded for .2mL 10% sucrose on a FR1 schedule of reinforcement with 40s time out in daily 2-h sessions. Active responses for sucrose decreased on the fourth day for males. In contrast, sucrose self-deliveries increased on the fourth day for females. For the seven subsequent sessions with no CBD pretreatment, active responses trended higher for females, while actual sucrose self-deliveries trended lower for males. Overall, these preliminary results indicate a sex difference in the effects of 20 mg/kg IP CBD on responding for 10% sucrose where females are more likely to increase responding and males decrease responding both during CBD treatment and for several days thereafter.

Disclosures: J. Grimm: None. **C. Bacon:** None. **K. Sanko:** None. **L. Jackson-Linvel:** None. **E. van den Dungen:** None. **A. O'Shea:** None. **B. Oliver:** None. **T. Trickett:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.11/M30

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Food restriction modulates amphetamine-induced locomotor activity by ghrelin and dopamine systems in the nucleus accumbens

Authors: *S. LEE[1], H. YOON[2], J.-H. KIM[3];
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Abstract: The mesolimbic dopamine system is activated by both natural rewards like food and drugs of abuse, indicating common neural substrates are involved in both appetite and addictive behaviors. Research has shown that there is a close link between ghrelin and dopamine in both appetite regulation and addiction. Food restriction is a natural way to increase ghrelin levels. This study examines the effects of both short- and long-term food restriction (FR) on the locomotor activity induced by amphetamine (AMPH). Rats were divided into three groups: normal feeding (NF), acute food restriction (aFR; 1-2 days), and chronic food restriction (cFR; 2 weeks). Following the establishment of these dietary conditions, acute AMPH was administered, and their locomotor activity was measured. Compared to the NF group, the cFR group, but not the aFR group, exhibited significantly higher locomotor activity in response to AMPH. Furthermore, injection of antagonists of dopamine D1 receptor (D1R) or ghrelin receptor (GHSR) either systemically or directly into the nucleus accumbens (NAcc) inhibited this effect. Next, rats were repeatedly exposed to AMPH, then they were administered with D1R agonist following NF, aFR, and cFR. Interestingly, sensitized locomotor activity was observed in both food restriction groups compared to NF group. These results indicate that food restriction positively modulates amphetamine-induced locomotor activity, and GHSR and D1R in the NAcc are involved mediating this process.

Disclosures: S. Lee: None. **H. Yoon:** None. **J. Kim:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.12/M31

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA-NIH DA055068
Mercer Seed Grant
Mercer Startup Grant

Title: Contextual cued palatable food seeking in male and female rats infused with the alpha1-adrenergic receptor antagonist Terazosin in the medial prefrontal cortex (mPFC)

Authors: *L. CALLAN[1], A. CAROLAND-WILLIAMS[1], U. MODI[2], J. BELFLOWER[2], J. BELFLOWER[2], A. PATEL[3], H. PATEL[3], G. LEE[3], J. C. GAINES[5], A. GHEIDI[4]; [1]Biomed. Sci., [2]Sch. of Med., [4]Dept. of Biomed. Sci., [3]Mercer Univ., Macon, GA; [5]Biomed. Sci., Mercer Univ. Sch. of Med., Macon, GA

Abstract: Research indicates that the brain's noradrenergic system plays a crucial role in resuming drug use after a period of abstinence. Blocking alpha1-adrenergic receptors in the medial prefrontal cortex (mPFC) can reduce cocaine-induced relapse. Less understood is the role of the adrenergic system in the reinstatement of food-seeking after forced abstinence. In this study, we explored the influence of the adrenergic system on the resumption of palatable food-seeking behaviors following forced abstinence. Male and female rats underwent training to self-administer sugar pellets for ten days, followed by a ten-day period of forced abstinence in their home cages. On the re-exposure day, we pharmacologically inhibited α1-adrenergic receptor in the mPFC using Terazosin (3 µg/0.5µl/hemisphere) immediately before contextual re-exposure. Vaginal lavage was performed on female rats to monitor their estrus cycles throughout the experiment. The results indicated that rats learned to prefer the active lever over the inactive one. Although rats could still distinguish between the active and inactive levers on the re-exposure day, there were no noticeable differences in the number of lever presses between the different groups or sexes. We are analyzing how quickly they press the lever and reviewing the data in fifteen-minute segments.

Disclosures: L. Callan: None. **A. Caroland-Williams:** None. **U. Modi:** None. **J. Belflower:** None. **J. Belflower:** None. **A. Patel:** None. **H. Patel:** None. **G. Lee:** None. **J.C. Gaines:** None. **A. Gheidi:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.13/M32

Topic: G.02. Reward and Appetitive Learning and Memory

Support: CAPES
DAAD
CNPQ

Title: Predictive value of rat pups' ultrasonic vocalizations on adult anxiety-like behavior and appetitive ultrasonic vocalizations evoked by cocaine

Authors: *C. DA CUNHA[1], N. CORDEIRO[2], J. A. POCHAPSKI[3], W. SANCHEZ[4], G. BALTAZAR[5], R. K. SCHWARTING[6], R. ANDREATINI[1];
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Abstract: Pup and adult rats use ultrasonic vocalizations (USVs) to express emotions. When separated from their mothers and litter, puppies emit 40-kHz USVs to elicit maternal care. Conversely, adult rats emit 50-kHz USVs in response to rewarding stimuli, stimulant drugs, and cues predicting rewards. Here we tested whether pup USVs predict positive or negative emotions in adult rats. Male and female Wistar pups were tested at 11 days old and again as adults. There was no sex difference in pup USV numbers. However, cocaine increased 50-kHz USVs and locomotor activity in adult females more than males. Cocaine also increased the proportion of step and trill USV subtypes, especially in females in diestrus. In adult males, the number USV emitted by pups predicted anxiety scores of adults in the elevated plus-maze test, but not in females. However, no correlation was found between puppy 40-kHz and adult 50-kHz USVs, regardless of drug treatment. It is possible that the 40-kHz USV emitted by pups predicted reduced anxiety-like behavior only for male rats because these calls elicit maternal care directed specifically to male pups. This suggests that maternal care exerts a positive impact on adult negative emotional states.

Disclosures: C. Da Cunha: None. **N. Cordeiro:** None. **J.A. Pochapski:** None. **W. Sanchez:** None. **G. Baltazar:** None. **R.K. Schwarting:** None. **R. Andreatini:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.14/Web Only

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant P20 GM113109-01A1
Johnson Cancer Research Center Undergraduate Research Award

Title: Nicotine associated contexts impair reinforcer devaluation in rats

Authors: O. WAREN[1], S. IMUZEI[1], J. KIM[1], E. DROTTZ[1], *C. PICKENS[2];
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Abstract: Objective and rationale: Addictive drug use is associated with abnormalities in human brain areas associated with devaluation. We previously examined whether prior nicotine exposure would impair goal-directed action in the devaluation task. We trained the rats that responses to two lever+cuelight compounds would earn two different reinforcers, and then tested the rats for devaluation with a levers associated with one reinforcer paired with a cuelight that predicted the other reinforcer. In this previous study, we found that male rats exhibited impaired devaluation if trained/tested in the presence of nicotine-paired cues, but not if nicotine had been paired with a different context. In the current study, we examined whether this cue-induced impairment can be overcome by allowing for compensation between strategies (by having congruent information indicated by the lever and cuelights). Methods: We gave adult Long Evans rats subcutaneous injections paired with 20-minute exposure to 2 distinction behavioral contexts. Rats in the Nicotine-Paired groups received 0.21 mg/kg nicotine paired with the behavioral conditioning chambers and saline paired with an alternative chamber. Rats in the Nicotine-Unpaired groups received saline paired with the conditioning chambers and nicotine paired with an alternative chamber. Rats in the Saline groups received saline paired with both contexts. The rats received exposures to each chamber (with the appropriate injections) prior to operant behavioral training with responses to a left lever+left steady cuelight earning precision pellets and responses to a right lever+right flashing cuelight earning sucrose pellets. The rats then received satiation on one of the two food pellets prior to a choice test in which both levers+cuelight compounds were available in order to assess whether prior nicotine exposure (either paired with the training/testing context or regardless of training/testing context) would impair devaluation. Results: We found that goal-directed action in the devaluation task was impaired in the Nicotine-Paired groups (both male and female) but was not impaired in the Nicotine-Unpaired group. Conclusions: We found that nicotine-paired environmental cues can lead to impaired goal-directed action in the devaluation task even at doses that do not impair goal-directed action regardless of the training/testing context, in accord with our previous research. However, we found no evidence that this devaluation impairment is overcome or obscured by allowing for compensation in the strategies to support goal-directed action by providing redundant cues that both indicate the same reinforcer.

Disclosures: O. Waren: None. **S. Imuzei:** None. **J. Kim:** None. **E. Drottz:** None. **C. Pickens:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.15/M33

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Role of CB2 Cannabinoid Receptor in the Regulation of binge-like eating of palatable food in adolescent mice

Authors: *L. RODRIGUEZ-SERRANO[1], M. CHAVEZ HERNANDEZ[2];
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Abstract: The CB2 cannabinoid receptor has been found in brain areas that are part of the reward system and has been shown to play a role in food intake regulation. The consumption of highly palatable foods (PF) involves learned habits and preferences through the reinforcing properties of powerful and repetitive rewards, which may lead to dysfunction of the neurobiological mechanisms that regulate eating behavior. However, the role CB2 cannabinoid receptor plays in binge-like intake has not yet been identified. In this regard, the present study aims to evaluate the effect of the administration of CB2 cannabinoid receptor agonist, antagonist or both, on binge-like intake of PF in adolescence in rats. We used thirty-two C57BL6/J mice (males) 4 weeks old and with 13-17 g of body weight in this research; all animals were housed individually and had ad libitum access to a standard diet (SD) and water; animal weight and SD food intake were manually recorded every 24h. Mice were randomly assigned to the following treatment groups: 1) “PF+VEH”, with PF and administration of vehicle; 2) “PF+AM630”, with PF access and administration (i.p.) of the antagonist of CB2 receptor; 3) “PF+HU308” PF access and administration (i.p.) of agonists of CB2 receptor; 4) “PF+AM630+HU308” PF access and coadministration (i.p.) of antagonist and agonists of CB2 receptor. All groups had 1h access to PF (Oreo® Cookies Nabisco®) according to intermittent diet protocol, with one-day access/ one-day no-access. PF and SD caloric intake, and PF binge index (defined as consuming ≥20% of total caloric intake per day during the 1h access to PF) were analyzed. Our results show that PF-HU308 reduced the consumption of binge intake of PF. Overall, these results suggest that activation of the CB2 receptor decreases the binge-like intake in adolescents mice and that it can lead to chronic overconsumption in conditions of non-homeostatic feeding that can be modulated for the CB2 receptor.

Disclosures: L. Rodriguez-Serrano: None. **M. Chavez Hernandez:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.16/M34

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R21 DA057073

Title: Postsynaptic dopamine signaling through cAMP and non-cAMP pathways: implications for associative learning

Authors: *N. H. SAMMUDIN, X. ZHUANG;
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Abstract: Understanding how our brains encode associations between environmental cues or actions and their outcomes is critical for guiding behavior and decision-making. This associative learning relies heavily on dopamine (DA) signaling. While presynaptic DA signaling is well-established, the mechanisms by which postsynaptic DA receptors modulate learning and influence behavior remain elusive. In this study, we explore the interplay of postsynaptic signaling pathways by focusing on the cAMP pathway as well as the alternative non-cAMP pathway, β-arrestin 2 (BA2), in order to elucidate their roles in associative learning. Our investigation spans Pavlovian and instrumental paradigms to provide insights into the distinct contributions of these pathways. Using mice lacking AC5 (AC5KO), previous work in our lab has demonstrated that AC5, the cAMP producing enzyme, is required for reward-prediction Pavlovian learning involving temporally specific discrete cues. Surprisingly, AC5KO showed intact contextual appetitive Pavlovian learning which led us to hypothesize that non-cAMP pathway(s) may be involved in such learning. We tested the involvement of the BA2 pathway. We found that mice lacking BA2 (BA2KO) displayed both contextual and discrete cue appetitive Pavlovian learning. However, they have subtle phenotypes that we are currently investigating. This finding also prompts further investigation into other postsynaptic signaling mechanisms underlying contextual learning. With instrumental learning paradigms, we examined AC5 and BA2 involvement in acquisition and extinction. Based on literature, we anticipated AC5KO mice to exhibit impaired acquisition and extinction due to disrupted cAMP signaling. While we observed delayed acquisition in AC5KO mice, they eventually performed similarly to controls, and surprisingly, they displayed normal extinction when their actions were not rewarded. D2 antagonist treatment or Gs DREADD activation in D2 neurons did not mimic extinction either. These data again suggest the involvement of non-cAMP pathway(s). We tested the role of the BA2 pathway; and BA2KO mice showed no impairments in either acquisition or extinction. These findings highlight the intricate role of the cAMP and non-cAMP pathways in post-synaptic processing of reward prediction error (RPE) and negative reward prediction error (NPE) fast signals as well as in processing slow dopamine signals during contextual appetitive Pavlovian learning.

Disclosures: N.H. Sammudin: None. **X. Zhuang:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.17/M35

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 1R25DA057802-01
NIH Grant R21 DA050822

Title: Impact of metformin on cocaine sensitization and alterations to AMPK and mTOR in mice

Authors: *K. L. BERTELSEN[1,2,3], R. ARULDAS[1,2], J. C. LEMOS[4,2], S. M. SPENCER[1,2]; [1]Pharmacol., Univ. of Minnesota, Minneapolis, MN; [2]Medical Discovery Team on Addiction, University of Minnesota, Minneapolis, MN; [3]Department of Neuroscience, University of Minnesota, Minneapolis, MN; [4]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) are evolutionarily conserved serine/threonine kinases involved in the regulation of energetic homeostasis at the organismal and cellular levels. Previous studies have shown each to be involved with some of the neuronal adaptations that underlie the enhanced locomotor response produced by repeat cocaine exposure (sensitization). Inhibition of mTOR via rapamycin produces dose-dependent inhibition of the induction and expression of sensitization and reduces cocaine-induced mTOR signaling in the nucleus accumbens (NAc). Likewise, our previous studies have shown pretreatment with the indirect AMPK-activator/ mTOR-inhibitor metformin produces behavioral effects in rats undergoing cocaine sensitization. Metformin potentiated the acute locomotor stimulating effects of cocaine but blocked the development of sensitization from repeated cocaine exposure in Sprague Dawley rats.
The objective of this study was to test whether metformin similarly reduced cocaine locomotor sensitization in male and female C57BL6/J mice from Jackson Laboratories. We also sought to quantify changes in AMPK & mTOR signaling following repeated cocaine exposure with and without metformin pretreatment. Metformin did not produce acute cocaine potentiation observed in rats. However, metformin did significantly block sensitization in female mice, and to a lesser extent (statistical trend) in male mice compared to littermate controls. These results suggest both sex and interspecies differences in the role of metformin in regulating cocaine-induced locomotion. Next, we examined total and phosphorylated (active) AMPK (Thr172) in the prefrontal cortex, NAc core and shell, and dorsal medial striatum following drug treatments. Despite metformin's ability to alter AMPK levels in other areas of the body, protein analysis found no changes to total or active AMPK levels in the explored brain regions. We are still in the process of analyzing samples for total and active mTOR (Thr2446 & Ser2481). In addition to protein analysis, we are also exploring metformin's impact on glutamate synaptic transmission within the NAc and its ability to block cocaine-induce plasticity at glutamatergic synapses.

Disclosures: K.L. Bertelsen: A. Employment/Salary (full or part-time):; University of Minnesota. **R. Aruldas:** A. Employment/Salary (full or part-time):; University of Minnesota. **J.C. Lemos:** A. Employment/Salary (full or part-time):; University of Minnesota. **S.M. Spencer:** A. Employment/Salary (full or part-time):; University of Minnesota.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.18/M36

Topic: G.09. Drugs of Abuse and Addiction

Title: The therapeutic effects of (2R,6R)-hydroxynorketamine in opioid use disorder

Authors: *M. LEHANE[1], C. DRINKUTH[2], G. C. SARTOR[1];
[1]Pharmaceut. Sci., Univ. of Connecticut, Storrs, CT; [2]Univ. of North Carolina, Chapel Hill, NC

Abstract: As the opioid crisis remains a major public health concern, new and effective treatments are needed to address opioid use, relapse and overdose mortalities. Researchers have recently turned their attention to psychedelics and dissociative drugs for the treatment of multiple psychiatric disorders, including substance use disorders. For example, ketamine has been shown to produce rapid-acting antidepressant effects, and recent results indicate that ketamine may be an effective treatment for opioid use disorder (OUD). However, the use of ketamine for OUD is limited due to its dissociative properties and misuse potential. On the other hand, (2R,6R)-Hydroxynorketamine (HNK), a ketamine metabolite, has also exhibited therapeutic effects in preclinical models of stress, depression and pain. Unlike ketamine, HNK lacks misuse potential, indicating a potentially safer treatment option. Recently, we found that HNK (30 mg/kg) attenuated the reinstatement of oxycodone conditioned place preference without altering locomotor activity in male and female mice. HNK (10 or 30 mg/kg) also alleviated somatic symptoms of withdrawal and global withdrawal scores 24 hr after the last oxycodone exposure. In new data, we found that HNK (10 mg/kg) and low-dose ketamine (10 mg/kg) alleviated depressive-like behavior of male and female mice during oxycodone withdrawal. To narrow down the neural mechanism of HNK's therapeutic effects, we identified multiple brain regions and subregions altered by HNK (10 or 30 mg/kg) and low-dose ketamine (10 mg/kg) in oxycodone-dependent mice using c-Fos immunohistochemistry. In ongoing experiments, we are analyzing transcriptomic and cell type-specific effects of HNK and low-dose ketamine during oxycodone withdrawal. Together, these experiments demonstrate the therapeutic effects of HNK in animal models of OUD, allowing for future experiments to investigate behavioral, cellular, and molecular effects of HNK in advanced models of OUD.

Disclosures: M. Lehane: None. **C. Drinkuth:** None. **G.C. Sartor:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.19/M37

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA ZIA000069

Title: (s)-ketamine decreases heroin seeking in rats

Authors: *M. R. LEVINSTEIN[1], R. C. BUDINICH[1], O. SOLÍS CASTREJÓN[1], C. A. ZARATE, Jr.[2], Y. SHAHAM[1], M. MICHAELIDES[1];
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Abstract: (R,S)-ketamine, a racemic mixture made of (R) and (S) enantiomers, has been used for decades as an analgesic and anesthetic. More recently, it has been used as an antidepressant. Further, (S)-ketamine is an FDA-approved pharmaceutical for treatment-resistant depression and depression with suicidal ideation. (S)-ketamine is regarded as a noncompetitive N-methyl-D-aspartate receptor antagonist, but it also binds to and activates the mu opioid receptor (MOR) in vivo. We recently showed that this interaction with MOR drives its abuse liability and that repeated administration of (S)-ketamine decreases subsequent heroin reinforcement.
We implanted adult rats with jugular vein catheters and then infused them with saline or (S)-ketamine for an hour a day for 1 or 8 days. Rats were euthanized 24 hours or one week after the last infusion. MOR density and function were the quantified. (S)-ketamine significantly decreased the MOR density and function after 8 days of infusions. These decreases were closer to baseline after one week.
Another group of rats were catheterized and underwent intravenous self-administration (IVSA) of heroin. They were then tested for heroin seeking and then divided into groups to receive 8 days of saline or (S)-ketamine. 24 hours and one week after the last infusion, the rats again were tested for heroin seeking. Rats acquired heroin IVSA at a unit dose of 100 μg/kg/infusion and increased their infusions once the unit dose was decreased to 50 μg/kg/infusion. Rats that received (S)-ketamine infusions significantly decreased their heroin seeking compared to rats infused with saline; however, this difference was only present at the 24 hour test.
In another cohort of rats, we implanted optic fibers coated in a mixture of the dopamine sensor, AAV9-hsyn-GRAB$_{DA}$, into the nucleus accumbens. We plan to inject the rats with (S)-ketamine and record dopamine transients.
Our findings indicate that (S)-ketamine induces transient MOR desensitization. Additionally, (S)-ketamine decreases heroin seeking indicating it may have potential for treatment of opioid use disorder.

Disclosures: M.R. Levinstein: None. **R.C. Budinich:** None. **O. Solís Castrejón:** None. **C.A. Zarate:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); coinventor on a patent for the use of ketamine in major depression and suicidal ideation, coinventor on a patent for the use of (2R,6R)-hydroxynorketamine (HNK), (S)-dehydronorketamine and other metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain, coinventor on a patent application for the use of (2R,6R)-HNK and (2S,6S)-HNK in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. **Y. Shaham:** None. **M. Michaelides:** 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.; AstraZeneca, Redpin Therapeutics, Attune Neurosciences.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.20/M38

Topic: G.09. Drugs of Abuse and Addiction

Support: P30 DA013429 (EMU)

Title: The Effects of Ketamine on Methamphetamine Withdrawal-Induced Anxiety and Drug-seeking Behaviors in Rats

Authors: *M. G. GHILOTTI[1], E. M. UNTERWALD[2], D. STERN[3], R. PETRILLI FORTUNA[4];
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Abstract: Recently, the recreational and prescription use of methamphetamine and its derivatives has risen among the youth and adult populations. In addition to facilitating dopamine neurotransmission, N-methyl-D-aspartate receptors (NMDARs) are activated indirectly by methamphetamine through the release of glutamate from glutamatergic neurons. Ketamine noncompetitively blocks NMDARs. Thus, we hypothesized that ketamine may be a potential therapeutic method to treat methamphetamine use disorder. This was explored using a rodent model of methamphetamine self-administration. Male rats underwent methamphetamine or saline IV self-administration for 10 sessions with tone and light cues, then 10 sessions of extinction training, followed by tests for cue and drug reinstatement. Anxiety-like behaviors were measured 48-hr after methamphetamine self-administration and again after the 10-day extinction period. During extinction only, rats received 5mg/kg ketamine or saline IP injections daily before entering the operant chambers. The findings from the first set of anxiety-like behavioral measurement tests are congruent with existing literature; methamphetamine withdrawal increased anxiety-like behaviors on the elevated plus maze and open field test compared to rats that self-administered saline. Moreover, anxiety-like behaviors remained elevated in the vehicle group after the extinction period, while anxiety was significantly attenuated in rats that received ketamine during extinction. The data from drug-induced reinstatement tested six days after the last ketamine extinction session showed a significant reduction of active lever presses for methamphetamine by rats treated with ketamine during extinction. NMDA and AMPA receptors were measured in brains harvested 24-hr after the reinstatement session. In the basolateral amygdala, NMDA and AMPA receptor subunits were significantly lower in rats that self-administered methamphetamine and this reduction was partially rescued by ketamine. These findings demonstrate that ketamine reduced anxiety-like behaviors produced by methamphetamine withdrawal and attenuated methamphetamine-seeking behavior.

Disclosures: M.G. Ghilotti: None. **E.M. Unterwald:** None. **D. Stern:** None. **R. Petrilli Fortuna:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

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Program #/Poster #: PSTR475.21/M39

Topic: G.09. Drugs of Abuse and Addiction

Support: DOST PCHRD DOST2020-04-A1-265

Title: Exercise reverses the effects of repeated toluene exposure in rats

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Abstract: Inhalant use is a significant problem in adolescents worldwide, especially in Filipino street children. Chronic use of inhalants can cause persistent behavioral impairments that need to be addressed with accessible, low-cost treatments. Exercise during abstinence has been shown to reverse toluene-induced memory deficits and attenuate locomotor sensitization to toluene (Mercadillo et al., 2019; Oros-Gonzalez et al., 2024), but its effect on other behaviors has not been examined. Last year, we reported that repeated inhalation of 3000 ppm toluene increased conditioned place preference (CPP) and impaired social novelty preference during abstinence. Toluene also increased locomotion in males, but not in females (Carampel et al., SfN 2023; Asis et al., SfN 2023). Here, we report that daily voluntary wheel running (4h/d) during abstinence (D1 to D7) significantly reduced CPP (one-way ANOVA: p=0.038; CPP score D8: Tol-Sed - 0.47, Tol-Run - 0.37, p=0.029). Wheel running also restored social novelty preference (social novelty score: Tol-Sed - 0.56, Tol-Run - 0.65; one-sample t-test vs. 0.5 with Bonferroni correction: Tol-Sed - p=0.220, Tol-Run - p=0.002) and reduced locomotion (one-way ANOVA: p=0.006; distance traveled: Tol-Sed - 77.34, Tol-Run - 62.17, p=0.007). In a separate group of rats, we tested the effects of repeated toluene on an appetitive reversal learning task (bar pressing for sucrose pellets) during abstinence. We found that prior toluene did not impair learning in an easy reversal task (0% vs. 75% reinforcement) but slowed learning in a more difficult reversal (75% vs. 20%) (two-way RM ANOVA: group - p=0.047; minute - p<0.001, interaction - p=0.947). We have yet to examine the effect of exercise on reversal learning impairments. These data suggest that exercise (and also N-acetylcysteine, see Carampel et al., this conference) may address the persistent social and cognitive deficits seen in inhalant users. We are now performing cFos immunofluorescence to determine the extent to which exercise can restore brain activity to its pre-addiction state.

Disclosures: J. Asis: None. **J.C. Munar:** None. **A. Carampel:** None. **C. Gregorio:** None. **L. Dalmacio:** None. **G.J. Quirk:** None. **R. Cena-Navarro:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.22/M40

Topic: G.09. Drugs of Abuse and Addiction

Support: DOST PCHRD DOST2020-04-A1-265

Title: N-acetylcysteine reverses the effects of repeated toluene exposure in rats

Authors: *A. CARAMPEL[1], J. C. MUNAR[2], J. ASIS[1], C. GREGORIO[3], P. MEDINA[4], G. J. QUIRK[2], R. CENA-NAVARRO[2];
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Abstract: Inhalant (toluene) use disorder (IUD) mainly affects adolescents and is especially prevalent among Filipino street children. Currently, there are no approved pharmacological treatments for IUD. N-acetylcysteine (NAC) and melatonin are two affordable, over-the-counter medications that have been shown to decrease drug-seeking in other substance use disorders, but have never been tried with toluene. Last year, we reported that repeated inhalation of 3000 ppm toluene increased conditioned place preference (CPP) and impaired social novelty preference during abstinence. Toluene also increased locomotion in males, but not in females (Carampel et al., SfN 2023; Asis et al., SfN 2023). Here, we report that daily NAC injections (100 mg/kg I.P.) during abstinence (D1 to D8) significantly reduced CPP (two-way RM ANOVA: significant main effect of time $p < 0.001$ and time x group interaction $p = 0.018$; CPP score: D1 - 0.54, D8 - 0.39, $p < 0.001$). However, in females (but not in males), a similar effect was observed with saline injections (two-way RM ANOVA: significant main effect of time $p < 0.001$; CPP score: D1 - 0.56, D8 - 0.42, $p < 0.001$). NAC also restored social novelty preference (social novelty score: Tol-Sal - 0.59, Tol-NAC - 0.67; one-sample t-test vs. 0.5 with Bonferroni correction: Tol-Sal $p = 0.026$, Tol-NAC - $p < 0.001$). Lastly, NAC decreased locomotion in males (one-way ANOVA: $p = 0.011$; distance traveled: Air-Sal - 62 m, Tol-NAC - 46 m, $p = 0.012$). Melatonin had no effect on any of these behaviors. Overall, NAC treatment (and also exercise, see Asis et al., this conference) during the abstinence period can reverse persistent toluene-induced behavioral deficits. We are now performing cFos immunofluorescence and transcriptomic analysis to determine the extent to which NAC can return brain functioning to its pre-addiction state.

Disclosures: A. Carampel: None. **J.C. Munar:** None. **J. Asis:** None. **C. Gregorio:** None. **P. Medina:** None. **G.J. Quirk:** None. **R. Cena-Navarro:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.23/N1

Topic: G.09. Drugs of Abuse and Addiction

Support: Göteborgs Läkaresällskap (GLS-999159, GLS-960721)
Wilhelm och Martina Lundgrens Vetenskapsfond (2022-4085)
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Fredrik och Ingrid Thurings Stiftelse (2020-00607)
Governmental support under the LUA/ALF agreement

Title: Accumbal glycine receptors as a new pharmacological treatment target for Alcohol use disorder - a translational study on systemic glycine treatment in rats and humans

Authors: *Y. OLSSON[1,2,3], K. DANIELSSON[1], M. ERICSON[4], B. SODERPALM[1,2];
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Abstract: Alcohol Use Disorder (AUD) is a brain disorder that involves perturbations of brain dopamine (DA) systems. Pharmacotherapies that target mechanisms by which alcohol interferes with the DA system may improve AUD treatment. Previous studies indicate that alcohol targets glycine receptors (GlyR) in the nucleus Accumbens (nAc) that inhibit γ-aminobutyric acid (GABA)-ergic projections to the ventral tegmental area, ultimately leading to increased DA release in the nAc. Local perfusion into the nAc with the endogenous GlyR agonist glycine raises basal DA levels, attenuates alcohol-induced DA release in the nAc and reduces alcohol intake in rats. In humans, glycine treatment has been shown to be safe for other indications than AUD. This translational study examines if systemic glycine treatment alters (I) nAc glycine and DA levels and alcohol intake in rats and (II) serum glycine levels, alcohol-induced craving and alcohol intake in individuals with AUD.The effects on alcohol intake and glycine and DA levels in the nAc were examined following treatment with glycine 200, 400 and 800 mg/kg i.p., using a two-bottle, free-choice alcohol intake paradigm and *in vivo* microdialysis in 65 male Wistar rats. In humans, 48 subjects with AUD completed a double-blind, placebo-controlled study that entailed five days of treatment with glycine 120 mg/kg p.o. followed by an alcohol-challenge experiment in which participants could choose to self-administer standardized alcoholic drinks. Results were evaluated by a one-way or two-way ANOVA or a Mann-Whitney test, followed by post-hoc analyses when applicable.In rats, glycine treatment i.p. reduced alcohol intake, raised nAc glycine in a dose-related manner and raised DA levels in a sub-population of animals defined as DA responders. In AUD participants, glycine treatment was well-tolerated and raised serum glycine levels to 125% but did not alter alcohol intake or alcohol-induced craving in the alcohol challenge experiment.Conceivably, the reduced alcohol intake in rats is achieved by the systemic glycine treatment enhancing nAc DA transmission, thereby alleviating a hypothesized hypodopaminergia and negative reinforcement to drink. The lack of translation to alcohol consumption in a lab setting in AUD participants may be due to insufficient dose or CNS penetrance, discrepancies between the studies in prior exposure to alcohol and in how alcohol

consummatory behavior was evaluated, or species differences in how GlyR activity influences reward processes. Further studies are warranted to establish whether pharmacological interventions that target nAc GlyRs may constitute a new treatment principle for AUD.

Disclosures: Y. Olsson: None. **K. Danielsson:** None. **M. Ericson:** None. **B. Soderpalm:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.24/N2

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R01-DA056331
NIDA R01-DA056675
University of Minnesota Interdisciplinary Doctoral Fellowship

Title: Development of domain-selective inhibitors of the angiotensin-converting enzyme for modulation of Met-enkephalin-Arg-Phe signaling in the brain

Authors: *F. HANAK[1], S. S. MORE[2], K. E. BERNSTEIN[3], P. E. ROTHWELL[1];
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Abstract: Previous work from our group has shown that the angiotensin-converting enzyme (ACE) regulates synaptic transmission in the nucleus accumbens, a brain region involved in substance use disorders (SUDs). ACE cleaves Met-enkephalin-Arg-Phe (MERF), an endogenous opioid peptide that binds to mu-opioid receptors to regulate neuronal activity. The two catalytic domains of ACE are functionally and structurally distinct, with the C-terminal domain being the primary target for most ACE inhibitors designed for cardiovascular disease treatment, and the N-terminal domain being less explored. With the goal of developing an ACE inhibitor for SUD treatment without cardiovascular side effects, we investigated whether N-domain inhibition is sufficient to elevate accumbal MERF concentrations. Acute brain slices containing intact nucleus accumbens tissue were taken from adult mice and incubated in artificial cerebrospinal fluid (ACSF) containing high-concentration KCl to stimulate neurons and cause secretion of neuropeptides, and RXP 407, a selective inhibitor of the ACE N-domain. After incubation, extracellular fluid was collected and analyzed using liquid chromatography tandem mass spectrometry. RXP 407 elevated MERF concentrations in a dose-dependent manner, up to 131% higher than baseline. To confirm the involvement of the N-domain in the observed effect, we repeated the experiment in N-domain knockout (NKO) mice, and observed a lack of effect at the same concentrations of RXP 407. These results suggest that N-domain ACE inhibition is sufficient to elevate accumbal MERF concentrations. To further interrogate the role of the N-domain in MERF degradation, we compared the degradation of MERF in brain tissue of NKO mice, C-domain knockout (CKO) mice, and their wild-type (WT) littermates by incubating

accumbal tissue slices in ACSF saturated with MERF, and measuring its degradation product, met-enkephalin. NKO mice exhibited a significantly lower rate of met-enkephalin production compared to their WT littermates, whereas there was no difference between CKO mice and their WT littermates, suggesting that the N-domain of accumbal ACE degrades MERF more efficiently than the C-domain. All experiments were performed using mice of 8 to 22 weeks of age, with an N of 8 to 10 (4-5 males and 4-5 females). Taken together with other ongoing work by our group, which shows that administration of the ACE inhibitor captopril elevates accumbal MERF concentrations and attenuates fentanyl reward in mice, we present an exciting opportunity to develop novel inhibitors of the ACE N-domain for the treatment of SUDs with minimal off-target effects.

Disclosures: F. Hanak: None. **P.E. Rothwell:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.25/N3

Topic: G.09. Drugs of Abuse and Addiction

Title: In silico identification of small molecule agonist binding sites on KCC2

Authors: A. B. AMENDOLARA, J. W. MINER, ***A. J. PAYNE**;
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Abstract: Potassium-Chloride Cotransporter 2 (KCC2) is the principal neuronal protein that maintains the low intracellular Cl^- levels essential for the majority of synaptic inhibition in the central nervous system. Dysregulation of KCC2 expression leads to decreased inhibitory tone in the central nervous system and concomitant hyperexcitability. KCC2 expression changes are also associated with a number of major disease states, including epilepsy, neuropathic pain, Rett Syndrome, spinal cord injury, and several others. Recent studies also suggest that KCC2 dysregulation may be important in substance use and dependence, making KCC2 an attractive target for treating many neurological conditions. Until recently, no direct agonists for KCC2 had been identified. The novel direct KCC2 agonist, VU0500469, was recently identified experimentally; however, no binding sites were identified or characterized. The goal of this work is to identify likely binding sites of this protein-ligand pair via computer simulation to pave the way for the discovery of novel KCC2 agonists. A 3D model of human KCC2 was obtained from the RCSB Protein Databank. VU0500469 was reconstructed manually. Using the PrankWeb interface, a structural binding pocket identification was performed with P2Rank. Blind, semi-flexible docking of the ligand, VU0500469, and KCC2 was performed using QVina-W and GNINA. Geometric, template-free binding site prediction with P2Rank yielded 27 potential binding pockets. GNINA was set to produce nine outputs, resulting in 18 total conformations. QVINA-W was set to produce 20 outputs. To aggregate these simulation results and determine likely binding sites, outputs from all three simulations were overlayed and visualized in PyMol,

looking for overlapping conformations and/or pockets. Sites with at least two overlapping results were selected as probable binding sites for further investigation. Only one site was identified by all three simulations. This was considered the most promising binding site. Inputs for the molecular dynamics simulation were generated using CHARMM-GUI and passed to CHARMM. The binding sites identified here may represent targets for the development of additional KCC2 agonists. We anticipate that this work will make additional studies possible that will lead to new therapies for some of the many neurological disorders associated with KCC2.

Disclosures: A.B. Amendolara: None. **J.W. Miner:** None. **A.J. Payne:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.26/N4

Topic: G.09. Drugs of Abuse and Addiction

Title: Effects of methylphenidate and R-modafinil on impulsive choice decision making in rats.

Authors: *Y. CHAE[1], H. SHEN[1], E. HANS[1], G.-H. BI[2], Z.-X. XI[2], Y. YANG[1];
[1]Neuroimaging Res. Br., Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Mol. Targets & Medications Discovery Br., Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Methylphenidate (MPH) is an FDA-approved psychostimulant used to treat attention-deficit/hyperactivity disorder (ADHD), characterized by symptoms of inattention, impulsivity, and hyperactivity. Despite its widespread use, there is ongoing debate on its impact on impulsivity. On the other hand, modafinil and R-modafinil are FDA-approved wakefulness-promoting agents for narcolepsy. Clinical observations have indicated potential cognitive enhancement properties of modafinil, leading to its off-label use as a "smart drug". Additionally, modafinil and R-modafinil have shown promise in reducing drug-taking and seeking behavior, as well as mitigating impulsivity in patients with pathological gambling, methamphetamine dependence, and alcohol dependence. This study aims to assess whether modafinil or R-modafinil holds therapeutic potential for ADHD treatment. Male adult rats were trained for the reward delay-discounting task (DDT), a well-established animal model for evaluating impulsive decision-making. Rats were categorized into high or low-impulsive groups based on their performance in DDT. The effects of MPH and R-modafinil on impulsive decision-making were assessed in each group. To determine the molecular targets underlying R-modafinil, we observed the effects of cocaine, JJC8-091, and desipramine on DDT. MPH (2.5, 5.0, 10 mg/kg, i.p.) demonstrated no significant effects on low-impulsive rats (n=11) but increased impulsivity in high-impulsive rats (n=10) in a dose-dependent manner. Conversely, R-modafinil (10, 30, 100 mg/kg, i.p.) exhibited an opposite pattern. It increased impulsivity in low-impulsive rats (n=11) while having no significant effect on high-impulsive rats (n=10). Furthermore, systemic administration of cocaine (3, 10, 15, 20 mg/kg, i.p.) or JJC8-091 (10, 20, 30 mg/kg, i.p.) had no effect in both groups of rats, while desipramine (1, 3, and 10 mg/kg, i.p.) increased impulsivity in

both low and high-impulsive rats. The findings suggest that 1) MPH may not offer therapeutic benefits in reducing impulsivity in treating ADHD; 2) R-modafinil, despite its efficacy in treating substance use disorders, appears to increase impulsivity in low-impulsive subjects, suggesting that we should be cautious when using R-modafinil as an off-label "smart drug" drug; and 3) as desipramine, a selective norepinephrine transporter (NET) inhibitor, produced similar effects as MPH and R-modafinil, it is suggested that a NET-related mechanism may underlie the action of MPH and R-modafinil in impulsivity. Further research is needed to test this hypothesis.

Disclosures: Y. Chae: None. **H. Shen:** None. **E. Hans:** None. **G. Bi:** None. **Z. Xi:** None. **Y. Yang:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.27/N5

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Icelandic Technology Development Fund grant no. 2220781-601.

Title: L-type calcium channel blocker amlodipine for the treatment of ADHD: Validation using zebrafish and rodent models, Mendelian randomization and human genetic data

Authors: *K. KARLSSON, H. THORSTEINSSON;
Reykjavik Univ., Reykjavik, Iceland

Abstract: ADHDis a chronic neurodevelopmental disorder which significantly affects lifeoutcomes. Currently, we validate prior larval zebrafish findings of amlodipineas an ADHD treatment using model rats and zebrafish and human genetic data.Amlodipine reduced hyperactivity in the Open Field Test in SHR rats and reducedboth hyperactivity and impulsivity in the 5-Choice Serial Reaction Time Task in*adgrl3.1* mutant^{-} zebrafish. We show that amlodipine also passesthe blood brain barrier and reduces telencephalic activation. MendelianRandomization analysis using human genetic data revealed significantassociations between ADHD and genetic variations in the subunits of L-typecalcium channels (α1-C; CACNA1C, β1; CACNB1, α2δ3; CACNA2D3), and the genestargeted by amlodipine combined. Finally, we show that amlodipine mitigates keyADHD symptoms in a cohort of people with a high ADHD genetic liability. Givenits well-tolerated profile, its efficacy in mitigating both hyperactivity andimpulsivity across different species, coupled with genetic evidence from humandata, the potential utility of amlodipine as a novel treatment for human ADHDis compelling.

Disclosures: H. Thorsteinsson: None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.28/N6

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA R01 AA026589
NIAAA K01 AA023867
NIAAA R01 AA027760
NIAAA R21 AA027614
NIAAA R01 AA021491
NIAAA R01 AA029841
NIAAA T32 AA007456
COBRE P20 GM130414
NIMH K99 MH123673
NIGMS FI2 GM128622
NIDA R21 DA209966
NIDA R33 DA029966
NCI P30 CA030199
NIMH PDSP HHSN-271-2013-00017-C
MLPCN HG005033

Title: Development of Novel Negative Allosteric Modulators of CRFBP-CRF2 for Substance Use Disorders

Authors: *K. SHANKAR[1], C. L. HAASS-KOFFLER[2], T. FRANCIS[3], P. J. GANDHI[4], R. PATEL[5], C. K. NIELSEN[6], S. E. BARTLETT[7], A. BONCI[8], M. S. HEDRICK[9], A. S. LIMPERT[10], M. ROBERTO[11], N. COSFORD[12], D. J. SHEFFLER[13];
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Abstract: Substance use disorders (SUDs), including alcohol use disorder (AUD), remain a prevalent public health burden. Current pharmacological treatments for SUDs are still largely ineffective, requiring research into novel therapeutic targets. The stress system, mediated by corticotropin-releasing factor (CRF), plays a critical role in the development of SUDs/AUD. In the brain, CRF binds to both the CRF_1 and CRF_2 receptors with high affinity. While CRF_1 antagonism in preclinical studies has been shown to decrease anxiogenic and withdrawal-like behaviors, CRF_1 antagonists have not been successfully translated at the clinical phase.

Conversely, CRF_2 agonism has been shown to decrease ethanol consumption and ameliorate withdrawal-like behaviors in rodents, making CRF_2 a promising target for therapeutic development. CRF binding protein (CRFBP) is a 37 kD glycoprotein that interacts with CRF_2 to modulate drug-taking/seeking behaviors as well as potentiate NMDA-mediated excitatory postsynaptic currents in dopaminergic ventral tegmental area neurons; thus, CRFBP may play a role in SUD/AUD development. CRFBP undergoes spontaneous proteolytic cleavage into a 27 kD fragment that binds free CRF and a 10 kD fragment that is tethered to CRF_2. We have previously shown that this 10 kD fragment tethered to CRF_2 (CRFBP-CRF_2) potentiates CRF-mediated Ca^{2+} mobilization in the cell. As the CRFBP-CRF_2 protein-protein interaction has a potential excitatory function in neurons, we hypothesize that it may be a valuable target for pharmacological modulation of SUD/AUD. To test this, we developed a chimeric cell-based assay in which CRFBP (10 kD) is tethered to CRF_2, and agonism of the complex with CRF can be detected using a fluorescence-based calcium sensor. Using this assay, we performed a high-throughput screen of novel small molecule chemical probes and identified two structurally distinct compounds that act as noncompetitive disruptors of the CRFBP-CRF_2 complex and have no effect on CRF_2 function in the absence of CRFBP (10kD). Using these compounds, we have developed additional chemical probes to further investigate the role of negative allosteric modulation of CRFBP-CRF_2 *in vitro*, *ex vivo*, and *in vivo* in order to optimize orally active compounds suitable for proof-of-concept studies for SUD/AUD treatment.

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Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.29/N7

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01-DA-044311
NIH Grant F31-DA-057812
AFPE Regional Award

Title: Repurposing aripiprazole for anxiety reduction during nicotine withdrawal: Insights on transcription and affective behavior

Authors: *E. R. PRANTZALOS, K. A. MCLAURIN, J. R. TURNER;
Pharmaceut. Sci., Univ. of Kentucky, Lexington, KY

Abstract: Nicotine dependence and schizophrenia are highly comorbid disorders, with a complex interplay of genetic, neurobiological, and behavioral factors. Some antipsychotics used

to treat schizophrenia impact smoking habits and cessation ability. Repurposing existing antipsychotics may reduce clinical barriers by addressing both disorders simultaneously. This exploratory study investigates the repurposing of the antipsychotic aripiprazole (ARIP) for smoking cessation. We tested concurrent use of ARIP during nicotine exposure or 24-hour withdrawal (24hWD) in adult male and female mice (wildtype B6;129-ErbB4tm1Fej/Mmucd) to characterize genomic expression patterns within the medial prefrontal cortex (mPFC) and to determine the efficacy of ARIP in ameliorating WD symptomology. Mice treated with chronic saline, nicotine (18 mg/kg/day, s.c.), or 24hWD also received chronic daily injections of ARIP (2.5 mg/kg, s.c.) or vehicle. Anxiety-like response was measured via Open Field, immediately followed by tissue harvest for qPCR. Experimentation was replicated thrice for a total N of 60 (35 males, 25 females). Results were analyzed independently for each sex. ARIP treatment exhibited an anxiolytic-like effect during 24hWD in both males and females. Transcriptomic analyses indicate sex-specific changes in genes related to neuregulin signaling (Nrg3, ErbB4) and glutamatergic signaling (Grin1/2A/2B) upon ARIP administration during WD. These alterations correlated with observed behavior changes, providing a molecular basis for ARIP's effects. Linear regression analyses indicate a brain-behavior relationship, with increased center time (reduced anxiety-like behavior) corresponding to increased levels of gene expression of Nrg3, ErbB4, Grin1, and Grin2A in males but not females during 24hWD. To determine baseline sex differences in our genes of interest, we analyzed mPFC tissue from naïve mice (6 males, 6 females). Further, to identify whether acute ARIP alters any of the transcripts at baseline, we analyzed mPFC tissue of mice (12 males, 12 females) treated acutely (20min) with ARIP (2.5 mg/kg, s.c.). Neither sex nor acute ARIP impacted expression of any of the genes of interest. Our interdisciplinary findings highlight the promise of repurposing ARIP for smoking cessation. By targeting shared genetic factors and modulating anxiety-like responses, ARIP may offer a valuable treatment option for both nicotine-dependent individuals and those with comorbid schizophrenia. Understanding the underlying mechanisms will inform future clinical trials and personalized treatment strategies.

Disclosures: E.R. Prantzalos: None. **K.A. McLaurin:** None. **J.R. Turner:** None.

Poster

PSTR475: Neuropharmacology of Addiction and Potential Treatments

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR475.30/N8

Topic: G.09. Drugs of Abuse and Addiction

Support: DK138131
DK136810

Title: Glp-1 receptor agonist exendin-4 reduces optogenetically evoked dopamine in the nucleus accumbens

Authors: *J. CZARNY[1], J. G. WANG[2], A. V. KRAVITZ[3];
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Psychiatry, Washington Univ. in St. Louis, St. Louis, MO; [3]Washington Univ. In St Louis, Saint Louis, MO

Abstract: Glucagon-like peptide-1 (GLP-1) is an endogenous neuropeptide that has been implicated in altering the rewarding properties of substances such as drugs or palatable foods, potentially by modulating phasic dopamine (DA) release. Recent pre-clinical and clinical studies using GLP-1 receptor agonists have shown promise of novel treatment targets for disorders such as addiction due to these observed modulatory effects. However, the underlying neural mechanisms of GLP-1's effect on the reward system remain poorly understood. We aimed to address this gap in knowledge by utilizing in vivo fiber photometry to record changes in spontaneous and evoked dopamine activity in mice after a GLP-1 receptor agonist, exendin-4 (EX-4, 1ug/kg), was administered intraperitoneally. DAT-Cre mice simultaneously expressed optical dopamine indicator dLight1.2 in the nucleus accumbens and excitatory opsin Channelrhodopsin-2 in dopamine neurons originating from the ventral tegmental area. During recordings, spontaneous and optogenetically-evoked dopamine activity was measured pre- and post- injection. Following EX-4 administration, we observed a reduction in evoked fluorescence amplitude, suggesting that EX-4 reduces phasic dopamine release. This is consistent with known actions of GLP-1 agonists on inhibitory inputs to the VTA. Future work will investigate whether this reduction in phasic dopamine reduces addiction-like behavior in an oral model of oxycodone self-administration. Combined, these physiological and behavioral data could be critical in understanding the therapeutic potential of GLP-1 receptor agonists in treatment of addiction.

Disclosures: J. Czarny: None. **J.G. Wang:** None. **A.V. Kravitz:** None.

Poster

PSTR476: Motivation: Regulation of Aversive Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.01/N9

Topic: G.03. Motivation

Support: 5T32DA018926-18
R00DA041493
R21DA053462

Title: Relationships between fentanyl self-administration and risk-taking behavior in rats.

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[1]Univ. of Texas at Austin, Austin, TX; [2]Psychology, Univ. Of Texas At Austin Inst. For Neurosci., Austin, TX; [3]Univ. of Texas, Austin, TX; [4]Psychology, The Univ. of Texas at Austin, AUSTIN, TX

Abstract: Individuals with opioid use disorder (OUD) display impaired decision-making behavior and elevated risk taking. To understand the relationship between opioid use and

elevated risk taking, our lab employs a rodent model of decision making involving risk of explicit punishment (Risky Decision-making Task; RDT). In this task, rats choose between a small, safe food reward and a large food reward that is accompanied by increasing risk of mild footshock punishment. In Experiment 1, we examined whether individual differences in risk preference in the RDT predicted aspects of self-administration of the synthetic opioid fentanyl. Male Sprague-Dawley rats were characterized on the RDT and then underwent fentanyl self-administration (6 hours/day) for 21 days. Rats escalated their fentanyl intake during self-administration, and rate of escalation as well as overall fentanyl intake were inversely associated with risk preference. To explore the possibility that chronic opioid use leads to increased risk taking, male and female rats were trained on the RDT until stable behavior emerged and then underwent fentanyl self-administration (6 hours/day) or sucrose self-administration for 14 days. Rats remained undisturbed for 3 weeks, after which they were re-tested on the RDT to assess fentanyl-induced changes in risk taking. Relative to performance before self-administration, rats that self-administered fentanyl displayed an increase in risk taking, an effect that was absent in sucrose control rats. To determine whether this fentanyl-induced increase in risk taking could be attenuated, rats were given systemic injections of the selective dopamine D2 receptor (D2R) agonist sumanirole before being tested on the RDT. Sumanirole decreased risk taking in fentanyl exposed rats, suggesting that D2R activation may be a potential strategy for mitigating opioid-induced increases in risk taking. Together, these findings suggest that risk aversion may predispose an individual to developing OUD, while chronic opioid use consequently increases risk taking, leading to continued drug use. Lastly, these data suggest that this increase in risk taking can be mitigated by activating D2Rs. Future work will determine whether a similar inverse relationship between drug-naïve risk taking and aspects of fentanyl self-administration exists in females. Future studies will also explore the contribution of D2Rs to fentanyl-induced increases in risk taking in regions known to play a role in adaptive risk taking. Collectively, this work will provide important insight into the neurobehavioral mechanisms underlying the relationship between opioid use and altered risk taking.

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Poster

PSTR476: Motivation: Regulation of Aversive Behavior

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Program #/Poster #: PSTR476.02/N10

Topic: G.03. Motivation

Support: F31DA057112-0
R01DA55676

Title: Estrogenic contributions to female risk aversion

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Abstract: Decision making is a cognitive process in which individuals assess options varying in their expected rewards and associated costs. There are robust sex differences in decision making, particularly when decisions involve risk of negative consequences, with females exhibiting greater risk aversion than males. Prior work shows that the ovarian hormone estradiol is a critical mediator of phenotypical female risk aversion; however, the specific mechanism by which estradiol exerts its effect on decision making is unknown. Further, the contribution of progesterone is yet unexplored in the context of risky decision making. To address these gaps in knowledge, female Long-Evans rats (n=18) were trained in the Risky Decision-making Task (RDT) in which rats choose between a small, safe food reward and a large food reward that is accompanied by a variable probability of footshock punishment. After achieving stable behavioral performance, rats were ovariectomized (OVX) and re-tested in the RDT. Rats then received an estrogen receptor α (ERα) agonist (1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole, PPT) or an ERβ agonist (diarylpropionitrile, DPN) via subcutaneous injection. These drugs were administered daily following RDT testing using a randomized within-subject design (PPT, 1mg/kg; DPN, 1mg/kg; PPT+DPN, 1mg/kg; vehicle, sesame oil) for 7 days such that each rat received 7 days of each treatment with a minimum of 8 days between treatments. Rats also underwent control tests with these treatment conditions to assess potential changes in shock reactivity or food motivation. During each treatment and the successive washout period, estrous cycles were monitored. In a separate cohort of animals, the effect of progesterone (P4) on RDT performance was assessed using an identical within-subject design (P4, 0.6mg/0.1mL + 5% EtOH; vehicle, sesame oil + 5% EtOH). Administration of the ERα selective agonist PPT (alone or in combination with DPN) attenuated OVX-induced increases in risk taking, causing a decrease in risk taking. These data expand our understanding of hormonal regulation of female risk aversion and indicate that estradiol modulates female risk aversion via ERα activation.

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Poster

PSTR476: Motivation: Regulation of Aversive Behavior

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Program #/Poster #: PSTR476.03/N11

Topic: G.03. Motivation

Support: NIH R01 DA042820
Charles E. Kubly Mental Health Research Center

Title: Aversion encoding by nucleus accumbens D1 and D2 medium spiny neurons

Authors: *B. E. COTE[1], D. S. WHEELER[1], E. M. GRAFELMAN[2], L. VLACH[3], M. COOPER[2], H. HIX[1], J. R. MANTSCH[4], M. C. HEARING[2], R. A. WHEELER[2]; [1]Marquette Univ., Milwaukee, WI; [2]Biomed. Sci., Marquette Univ., Milwaukee, WI; [3]Neurosci., Marquette Univ., Milwaukee, WI; [4]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Previous work from our lab and others has found that aversive stimuli cause significant reductions in nucleus accumbens (NAc) dopamine and a corresponding increase in NAc neuronal activity. 90% of the neurons in the NAc are GABAergic medium spiny neurons (MSNs) that express either D1 or D2 dopamine receptor subtypes (approximately 5% express both) and have been thought to exert opposing influences on behavior. D1 MSN activity has been associated with reward, while D2 MSN activity has been associated with aversion. To investigate how aversion-induced changes in dopamine influence the excitability of MSN subtypes, we used *ex vivo* patch clamp electrophysiology to measure MSN activity changes in response to different dopamine concentrations. Preliminary data show that a high (100uM) concentration of dopamine increases the excitability of D1 MSNs and decreases the excitability of D2 MSNs. We also used *in vivo* fiber photometry to measure Ca^{2+} activity changes in these MSN subtypes during the experience of an aversive stimulus. Adora2 Cre+ (n=5) and D1 Cre+ (n=5) mice were injected with the Ca^{2+} sensor, GCaMP6f in the NAc and received a chronically implanted optic fiber. After recovery and viral expression, mice were then exposed to an intense 90dB white noise and a mild 72dB white noise (7dB above ambient noise) in different sessions. A 2 (noise) X 2 (genotype) X 2 (epoch) ANOVA revealed a significant noise X epoch interaction ($F(1,5) = 13.39$; $p<0.05$). Tukey's HSD revealed that calcium activity in both subtypes increased in response to intense ($p<0.05$) but not mild noise ($p>0.05$). The lack of a significant noise X genotype X epoch interaction indicated that D1 and D2 MSNs similarly encode aversive white noise. To further explore the encoding of aversion-related behavior in MSN subtypes, Adora2 Cre+ and D1 Cre+ rats received GCaMP6f and an optic fiber in the NAc. After recovery and expression, rats were trained in a negative reinforcement task. In daily sessions, rats were presented with an intense100dB white noise that could be terminated by a nose poke into an active port. Responding in an inactive port (counterbalanced) had no consequences. Initial findings are consistent with the prior experiment. Intense white noise presentation increased D1 MSN activity ($t(6) = 3.63$, $p<0.05$) and supported operant escape responses. The D1 MSN response to the termination of the white noise was a decrease in Ca^{2+} activity ($t(6)=3.40$, $p<0.05$). Ongoing experiments are examining the role of D2 MSN activity during negative reinforcement. Together, this work will further our understanding of the mechanism by which aversive experiences are encoded in the NAc and modulate behavior.

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Poster

PSTR476: Motivation: Regulation of Aversive Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.04/N12

Topic: G.01. Fear and Aversive Learning and Memory

Support: FFOR Foundation

Title: Amygdala projections to the dorsomedial striatum contribute to the balance between positive and negative reinforcement strategies

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Abstract: Appropriate control of action selection, a process mediated in part by cortical-basal-ganglia-thalamocortical loops, is fundamental for survival. Most studies in this domain have focused on behavioral strategies for obtaining positive outcomes. Here, we develop an operant task in mice that simultaneously encompasses action selection processes for obtaining positive outcomes (positive reinforcement) or the removal of aversive outcomes (negative reinforcement). Using tone-driven selection of positive or negative reinforcement choices, we studied the contribution of amygdala projections to dorsomedial striatum (DMS) in these distinct reinforcement strategies. Using retrograde and anterograde tracing, we described basolateral amygdala (BLA) projections along the antero-posterior DMS axis. Functionally, we performed single-unit recordings of BLA neurons, finding more robust trial-by-trial population modulation during positive reinforcement trials as compared to negative reinforcement. Opto-tagging of DMS-targeting BLA neurons via antidromic stimulation showed activity patterns that were largely representative of the broader BLA population. Finally, using optogenetic inhibition of BLA terminals in DMS, we find that disrupting this circuit biases animals towards negative reinforcement. Our results support a model whereby amygdala-striatal projections can bias choice according to positive or negative reinforcement strategy.

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Poster

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Topic: G.03. Motivation

Support: NIH Grant R01 DA048280
NIH Grant 1F31 DA058523
Charles E Kubly Mental Health Center

Title: The effect of chronic stress on nucleus accumbens dopamine encoding of escape behavior

Authors: *E. GRAFELMAN[1], B. COTE[1], L. VLACH[1], N. PADULA[1], K. ZIMOLZAK[1], P. BAARTMANS[1], E. GEISE[1], D. S. WHEELER[1], M. C. HEARING[1], J. R. MANTSCH[2], R. A. WHEELER[1];
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Abstract: Encounters with negative outcomes are marked by changes in an animal's emotional state and decision making. This often promotes adaptive behavior to avoid, alter, or escape an unpleasant environment. A considerable amount of evidence indicates that dopamine (DA) signaling in the nucleus accumbens core (NAcC) is an essential component of the decision-making process, in which affective and associative information influence motivated behavior. To address the role of mesolimbic DA in encoding aversive stimuli and to examine its relationship with motivated behavior, we measured NAcC DA using fiber photometry in a negative reinforcement design. Female and male Sprague Dawley rats (N=13 females, N=13 males) underwent surgery in which they received an infusion of AAV5-hSyn-dLight 1.2 into the NAcC and implantation of an optic fiber to the same location. Following recovery, rats were trained in daily sessions to press levers for the delivery of a sucrose pellet. After stable responding was reached on both levers at variable interval schedule (ranging from 30s to 150s), rats were transitioned to negative reinforcement. In this phase, a white noise (either intense (90dB) or mild (55dB)) was intermittently presented and responses on one lever (active lever, counterbalanced) terminated the white noise while responses on the inactive lever had no consequence. If no response was made, the white noise timed out after 60s. The next trial started 6s after a timeout or 11s after an active lever response. Intense white noise (but not mild white noise) significantly reduced DA signaling on the first day of negative reinforcement ($F(1,31)=22.62$, $p<0.001$ for intense, $p>0.95$ for mild). Consistent with this, animals exposed to intense white noise maintained responding on the active lever while rats exposed to mild white noise did not ($F(8,192) = 8.52$, $p <0.0001$). Ongoing studies are testing the effect of chronic stress on negative reinforcement and associated NAc DA signaling. Male rats (n=18) were either exposed to chronic variable stress (CVS; two heterotypic stressors/day for 14 days) or to control handling for the same duration, then tested in negative reinforcement with intense (90dB) white noise. Rats were tested first on a fixed ratio and then with a progressive ratio. Rats in this cohort that underwent CVS had higher break points in progressive ratio ($t(17)=3.18$, $p=0.006$). These data may indicate that stress increases sensitivity to aversive white noise and motivation to escape. Additional tests are measuring the effect of CVS on DA signaling in the NAc using dLight fiber photometry.

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Poster

PSTR476: Motivation: Regulation of Aversive Behavior

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Topic: G.03. Motivation

Support: MEXT KAKENHI 19H05002
JSPS KAKENHI 19K16248
JSPS KAKENHI 22K07329
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Title: A top-down neural circuit for overcoming fear and facilitating reward-seeking behaviors in environments with conflicting stimuli

Authors: *N. HITORA-IMAMURA[1,2], Y. HONSHUKU[1,2], C. SICILIANO[3,4], P. NAMBURI[4], K. M. TYE[5,4], Y. KURAUCHI[1], H. KATSUKI[1], H. NOMURA[6,2], T. AMANO[2], M. MINAMI[2]; [1]Dept. of Chemico-Pharmacol. Sci., Kumamoto Univ., Kumamoto, Japan; [2]Hokkaido Univ., Sapporo, Japan; [3]Pharmacol., Vanderbilt Univ., NASHVILLE, TN; [4]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [5]Systems Neurosci. Lab., Salk Inst. for Biol. Studies, La Jolla, CA; [6]Dept. of Cognitive Function & Pathology, Nagoya City Univ., Nagoya, Japan

Abstract: We are surrounded by various appetitive and aversive stimuli that positively motivate and negatively influence our behaviors, respectively. Overcoming fear is necessary to initiate and maintain seeking behavior to appetitive stimuli in environments where appetitive and aversive stimuli coexist. However, the neural mechanisms that regulate behavior in environments with conflicting stimuli are not well understood. To explore the neural pathways necessary to pursue goals without giving up, we utilized a behavioral paradigm in which mice aimed to obtain a sucrose solution in a context where they might receive electric foot shocks. Fiber photometry using the Ca^{2+}-sensitive fluorescent protein GCaMP6 showed that the neuronal pathway from the dorsomedial prefrontal cortex (dmPFC) to the dorsolateral/lateral periaqueductal gray (dl/lPAG) was activated when the mice approached the sucrose solution. Optogenetic activation and inhibition of the dmPFC-dl/lPAG pathway promoted and suppressed reward-seeking behavior, respectively, in the situation with conflicting stimuli. Interestingly, in a non-conflict situation, where mice could obtain a sucrose solution without fear of being shocked, neither optogenetic activation nor inhibition of the dmPFC-dl/lPAG pathway had any effect on reward-seeking behavior. Furthermore, the dmPFC-dl/lPAG pathway was activated at recovery from freezing behavior, and optogenetic inhibition of this pathway increased freezing time in the contextual fear conditioning test. These results suggest that dmPFC-dl/lPAG activity encourages animals to seek rewards in conflict contexts by suppressing fear responses. Overall, this study reveals a novel top-down neural mechanism by which the dmPFC-dl/lPAG pathway regulates the integration of fear and reward processing, shedding light on the complex interplay between negative and positive motivational states in shaping behavior.

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Poster

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Topic: G.03. Motivation

Title: Regulation of behavioral strategy in aversive environments by the ventral lateral geniculate nucleus

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Abstract: Animals' ability to flexibly choose from various responses to changes in their environment is a fundamental part of optimizing their chances of survival. These decisions crucially depend on context, internal state, and prior experience. The activity of the ventral lateral geniculate nucleus (vLGN), an inhibitory prethalamic nucleus, is modulated by prior experience and expectation of threat and exerts strong control over defensive behaviors. We are thus investigating the hypothesis that vLGN is a critical node for choosing between behavioral strategies in aversive contexts, such as staying safe from predators versus foraging for resources. Using optogenetics and fiber-photometry in freely behaving mice, we show that vLGN activity can dictate decisions regarding whether to stay in 'safety' or enter potentially aversive environments, such as the open arms of an elevated plus maze or leaving a shelter after experiencing an innately threatening visual stimulus. Importantly, manipulating vLGN activity affects exploratory behavior only in aversive contexts and does not influence exploratory drive or motivation more generally. Moreover, opto- and chemogenetic vLGN stimulation robustly rescue behavior in an acute corticosterone model of heightened anxiety, indicating that the regulation of defensive behaviors by vLGN is a function of anxiety-like state and may represent a potentially clinically-relevant treatment target. Finally, we investigated which upstream areas provide relevant information to vLGN. We find that signals from both cognitive cortical systems and affective subcortical systems converge in vLGN and impact mice's behavioral strategies in aversive contexts. Corticofugal layer V afferents from retrosplenial cortex, but not anterior cingulate cortex, modulate decisions on whether to depart from safety through vLGN. Additionally, inputs to vLGN from ventromedial hypothalamus have a powerful influence on mice's anxiety-like behavior. We propose that these inputs are integrated in vLGN to guide the selection of risk-related actions depending on the animal's needs, internal fear state, and prior experience.

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Poster

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Program #/Poster #: PSTR476.08/N16

Topic: G.04. Emotion

Support: Wellcome Trust Programme grant 224432/Z/21/Z

Title: Inhibition of dorsolateral prefrontal cortex projections to Area 32 blunts motivation and induces anxiety across a dorsoventral axis

Authors: *C. M. WOOD[1], M. FORT[1], R. BANAI TIZKAR[1,2], L. B. MCIVER[1], A. ROBERTS[1];
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Abstract: The dorsolateral prefrontal cortex (dlPFC) is considered part of a network contributing to many higher-order processes including working memory and attention. Recently it has become the target of non-invasive stimulation for the treatment of depression, effects that appear lateralised and are hypothesised to depend upon interactions with ventromedial prefrontal areas, such as subcallosal cingulate Area 25 and peri-genual area 32. Nonetheless, the direct involvement of the dlPFC in affective processes and their associated neural circuitry remains unknown. To examine this directly we surgically infused an AAV into dlPFC area 46 (dlPFC-46) enabling expression of the inhibitory hM4Di DREADD in CaMKIIa expressing excitatory projection neurons. Chemogenetic inhibition of dlPFC-46 and it's connections to the dorsal or ventral portions of medial prefrontal Area 32 (A32d/A32v) as well as subcallosal cingulate Area 25 (A25) were examined on a progressive ratio (PR) touchscreen task and human intruder test (HIT). These paradigms were selected to examine appetitive motivation and threat related behaviours, respectively. Inhibition of dlPFC-46 excitatory projections through systemic deschloroclozapine treatment (DCZ; 10ug/kg, intramuscular) blunted motivation through reduction in the number of responses on the PR task and increased threat responses to an unknown human. Inhibition of specific pathways from dlPFC-46 to A32d, A32v or A25, through direct infusion of DCZ (100nM) into the terminal regions prior to testing, revealed a dissociation of effects. Selective inhibition of the dlPFC-46 to A32d pathway reduced the number of responses in the PR task, whilst the A32v and A25 pathways were without effect. In contrast, heightened threat responses in the HIT were the result of inhibition of the dlPFC-46 to A32v pathway alone. These data indicate a dorsoventral functional axis of disrupted connectivity for dlPFC-46 that mediate motivational anhedonia and anxiety, separately. To examine issues of laterality, we selectively inhibited either the left, right or bilateral pathways between dlPFC-46 and A32d on the PR task. Selective inhibition of the left and bilateral dlPFC-46 to A32d pathways blunted the number of responses in the task, whilst inhibition of the right dlPFC-46 to A32d pathway had no effect. This provides evidence of functional laterality of dlPFC-46 in controlling appetitive motivated behaviour. Overall, these data demonstrate the regulation of appetitive motivation and threat-related behavior by dlPFC-46 projections to A32 in marmosets that may provide mechanistic insight into the treatment effects of modulating dlPFC function in humans.

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Poster

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Topic: G.03. Motivation

Support: DP220100049 from the Australian Research Council.

Title: Striatal mechanisms of punishment learning

Authors: *B. LIN[1], P. JEAN-RICHARD-DIT-BRESSEL[2], G. P. MCNALLY[1];
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Abstract: The role of dopamine and the dorsal striatum in appetitive instrumental learning is well studied but its role in instrumental punishment learning remains poorly understood. Reinforcement learning accounts identify punishment as the opposite of reward and so predict that punishers should reduce dopamine release in the striatum (i.e. punishment is equivalent to negative phasic prediction error) and increase the activity of dopamine 2 receptor-expressing neurons to support behavioral avoidance learning. To assess this, we used dLight fibre photometry to record dopamine binding in the dorsal striatum (dorsolateral [DLS], dorsomedial [DMS], tail [TS]) as well gCaMP fibre photometry to record activity of dopamine 1 receptor (*Drd1)* and dopamine 2 receptor (*Adora-2a*) neurons during punishment learning. Rats were trained to press two levers for food under a VI-30 schedule. Then one response was punished, via footshock, on an FR-10 schedule whereas the other response was not. There were action- related dopamine transients for both the punished and unpunished lever press. Punishment itself caused robust dopamine transients across the dorsal striatum. Within the DMS, punishment was associated with increased activity of *Drd1* neurons but only a transient activation of *Adora-2a* neurons during early and not later punishment sessions. Interestingly, punishment augmented both dopamine release and *Drd1* activity in DMS during reward retrieval. Taken together, these findings suggest that the profile of dopamine release and dopamine neuron activity during punishment learning is similar, not opposite, to instrumental reward learning. We suggest that during punishment, dopamine binding and *Drd1* activity in the DMS, report a teaching signal for instrumental learning that is unsigned with respect to the value of the outcome being learned about.

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Poster

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Topic: G.01. Fear and Aversive Learning and Memory

Support: DA046491
DA057954

Title: Melanin-concentrating hormone reduces learned helplessness and modulates layer 2/3 medial prefrontal cortex pyramidal neuron properties in male mice

Authors: *D. T. VAUGHAN[1,2,3], T. BARNHARDT[1], Y. H. HUANG[1,2];
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Abstract: Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder caused by exposure to trauma or stress. In PTSD and depression patients, sleep disruptions and insomnia are comorbid and positively correlate with symptom severity. Rapid eye movement sleep (REMS) is a potential therapeutic for the amelioration of PTSD symptoms and promotes resiliency to the disorder. This is consistent with the notion that REMS facilitates forgetting and remodeling the valence of an event. The medial prefrontal cortex (mPFC), an integrative hub involved in planning and adaptive control, is dysregulated in PTSD patients. The mPFC is known to be hyperactive in PTSD patients comorbid with depression, which has been recapitulated in mice using learned helplessness, a behavioral model for PTSD and depression. Melanin-concentrating hormone (MCH), predominantly released during REMS, regulates neuronal firing and synaptic transmission, thus providing a molecular substrate for REMS-regulated emotional memories. In this study, we tested if MCH can reduce learned helplessness in mice, and determined the role of MCH in modulating mPFC pyramidal neuron properties. Mice were exposed to inescapable shocks (360 shocks, 0.30mA, 1-3s variable duration, 1-15s variable interval) on two training days, and tested 24 hr later in a shuttlebox, where mice could escape the shocks (10 s, 0.15 mA) following a tone cue (5 s). The escape latency and number of failures were used to determine if the mouse was “helpless” or "resilient" (k-means, k=2). Following testing and before sleep onset (zeitgeber time 3), mice were given intranasal (IN) MCH (25ug/30uL), i.p. MCH receptor antagonist (TC-MCH 7C, 10mg/kg), or saline (i.p. or IN) and retested 24 hr later to determine changes in helplessness in relation to initial test results. IN MCH reduced helplessness (n=8, $p = 0.0016$, paired t-test). Further, to determine how MCH modulates layer 2/3 mPFC pyramidal neurons, we used patch-clamp slice electrophysiology. MCH (3 uM) application increased spontaneous inhibitory postsynaptic current (sIPSC) amplitude and frequency (n = 10 – 15 cells, One-way ANOVA, $p < 0.0001$), increased membrane resistance (n = 10 – 12 cells, Two-way repeated measures ANOVA, $F(4, 68) = 15.09$, $p < 0.0001$), and reduced the rheobase for action potential firing (n = 10 – 12 cells, Welch’s t-test, $p = 0.0319$). These effects were blocked by TC-MCH 7c (10uM). Together, these results implicate MCH in reducing stress-induced behaviors and demonstrate a role for MCH in regulating mPFC pyramidal neuron activities.

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Topic: G.01. Fear and Aversive Learning and Memory

Support: R01 DA052108
T32 DA007244

Title: High gamma (80 Hz) Optical Activation of the Infralimbic Cortex to Nucleus Accumbens Shell Pathway Alters Innate but not Learned Negative Affect in Female Rats

Authors: *E. GRABLIN[1], R. M. CARELLI[2];
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Abstract: Dysfunctional hedonic processing is associated with numerous psychiatric diseases including substance use disorders and depression. Understanding the basic neural mechanisms underlying aversive affective states can provide insight into treatment strategies aimed at restoring normal hedonic processing in psychiatric illnesses. Taste reactivity (TR) can be used to study negative affect in rat models. TR involves examination of appetitive and aversive orofacial responses to a tastant that is intraorally infused into the rat's mouth. In addition, TR can be used with conditioned taste aversion (CTA) to study the development of learned negative affect. CTA involves pairing a naturally rewarding sweet with a malaise-inducing agent, lithium chloride (LiCl), causing the sweet to become aversive. The infralimbic cortex (IL) to the nucleus accumbens shell (NAcSh) has been linked to negative aversive states in rats. For example, our lab showed that 20 Hz optical stimulation of IL to NAcSh pathway rescued learned aversive responses in male, but not female rats (Hurley and Carelli, *J. Neurosci*, 2020). We also reported a significant change in neuronal activity in the NAcSh at the high gamma (80 Hz) frequency range during CTA and quinine trials in female rats, that differed in males (Douton and Carelli, *Bio. Psyc. GOS*, 2023). In the current study, we examined the effects of high gamma (80 Hz) optical stimulation of the IL-NAcSh pathway on innate versus learned aversion in female rats. Female Sprague Dawley rats (9 ChR2, 9 mCherry) received either ChR2 (AAV-CaMKIIa-hChR2(H134R)-mCherry) or control virus (AAV-CaMKIIa-mCherry) injected bilaterally into the IL. Eight weeks later, the rats underwent a second surgery where optical fibers were implanted bilaterally into the rostral NAcSh, and an intraoral (IO) cannula was implanted. After recovery, rats underwent a naïve trial in which they received 30 IO infusions of 0.15% saccharin (3 sec/infusion) followed by an intraperitoneal injection of 0.3 M LiCl to induce CTA. 2 days later (test day) rats again received 30 IO infusions of saccharin, but each infusion was paired with simultaneous 80 Hz optical stimulation. Following extinction (5 days), rats received 30 IO infusions of quinine paired with simultaneous 80 Hz stimulation to study the effects of

stimulation on innate aversion. We found that 80 Hz stimulation did not alter CTA; however, optical stimulation decreased both appetitive and aversive responding and increased neutral responses during quinine trials. These results indicate that in females the IL-NAcSh pathway may not be involved in learned aversion, but it may play a complex role in innate aversion.

Disclosures: E. Grablin: None. **R.M. Carelli:** None.

Poster

PSTR476: Motivation: Regulation of Aversive Behavior

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR476.12/N20

Topic: G.01. Fear and Aversive Learning and Memory

Support: Dean's Opportunity Award
TCU/IS Grant 66054
SERC Grant

Title: Frustrative nonreward: role of outputs from the nucleus accumbens in reward downshift

Authors: C. W. HAGEN[1], J. SUAREZ[2], ***M. R. PAPINI**[2];
[1]Texas Christian Univ., Fort Worth, TX; [2]Psychology, Texas Christian Univ., Fort Worth, TX

Abstract: Frustrative nonreward is a negative emotional state induced by unexpected reductions in reward quality or quantity and often modeled through reward downshift procedures. Recent studies have implicated components of the basal ganglia (BG) in modulating the response to a sucrose reward downshift in which chemogenetics were used to selectively activate specific areas. The present experiments implemented a Cre-dependent double-infection DREADD procedure to identify the role of specific pathways within the BG. Three outputs of the nucleus accumbens (NAc) were targeted: the globus pallidus externus (GPe), the globus pallidus internus (GPi) and the ventral pallidum (VP). Male Wistar rats (90 days old) received bilateral infusions in the NAc with a viral vector construct carrying the excitatory Cre-dependent DREADDs [AAV5 pAAV-hSyn-DIO-hM3D(Gq)-mCherry] which contained a red fluorescent reporter (mCherry) and a DNA fragment for the engineered muscarinic receptor M3. Retrogradely transported viral vector constructs (AAV9-hSyn-eGFP-Cre) carrying the Cre protein and a green reporter (eGFP) were infused bilaterally into one of the outputs of the NAc (GPe, GPi, or VP). Thus, only projection neurons containing the Cre protein expressed the excitatory DREADD receptors (hM3Dq) in the NAc, as assessed via fluorescent microscopy. Groups infused with a control virus were also included. All animals received systemic injections of clozapine N-oxide (CNO) or vehicle during four 32-to-2% sucrose downshift sessions. Separate unshifted groups of animals were also tested using 32-to-32% or 2-to-2% sucrose. All animals were tested in the open field to assess motor effects. Chemogenetic excitation of the NAc-to-GPe pathway had no detectable effects on the response to reward downshift, whereas activation of either the NAc-to-GPi or NAc-to-VP pathway enhanced consummatory suppression, all in the absence of motor

effects in the open field. Preliminary data from unshifted controls show similar suppression after activation of the NAc-to-VP pathway, but not the NAc-to-GPi pathway, suggesting a motor component to the former pathway independent of reward downshift. These experiments are the first to identify specific pathways implicated in the neurobiological processes governing the response to frustrated nonreward.

Disclosures: C.W. Hagen: None. **J. Suarez:** None. **M.R. Papini:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.01/N21

Topic: G.03. Motivation

Support: NIH R01DA054094

Title: Tracing top-down and bottom-up pathways through the paraventricular thalamus in the sign-tracker/goal-tracker rodent model

Authors: *S. S. DESROCHERS, S. B. FLAGEL;
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Abstract: Cues in our environment usually guide appropriate behavior, however, they can also gain inordinate control over our actions. For example, the sight of drug paraphernalia may lead to craving and relapse in individuals with substance use disorders. This occurs following the attribution of incentive salience to the drug cue. We are able to study individual variability in the propensity to attribute incentive salience to reward cues in rodents using a Pavlovian Conditioned Approach (PavCA) paradigm, where a lever-cue predicts a food reward outcome. Rats deemed sign-trackers preferentially interact with the lever-cue, while goal-trackers tend to interact with the food magazine upon cue presentation. The behavior of sign-trackers is indicative of the attribution of incentive salience to the reward-predictive cue, such that the motivational value of the reward is transferred to the cue. Previous research has demonstrated that, in response to cue presentation, sign-trackers more strongly engage subcortical neural circuitry, while goal-trackers engage cortical neural circuitry. These bottom-up and top-down signaling mechanisms integrate at the level of the paraventricular thalamus (PVT), which sends output to the nucleus accumbens (NAc). PVT projections modulate dopamine release in the NAc, which is integral to the expression of sign-tracking behavior. However, we do not yet know how these projections interact anatomically to modulate sign- and goal-tracking behavior. Here, in adult male and female Sprague-Dawley rats, we developed a method to trace multisynaptic input/output pathways through the PVT, to examine how these pathways are differentially activated in response to cue exposure in sign- and goal-trackers. High titers of AAV1 serotype viruses can anterogradely travel over synapses, and, when combined with retrograde viruses, allow us to label cells in the PVT which receive input from either or both the lateral

hypothalamus (LH) and the prelimbic cortex (PrL), and output to the NAc Shell. In the present set of data, the labeled pathway from the LH-PVT-NAc appears to have minimal overlap with the PrL-PVT-NAc pathway at the level of the PVT, suggesting that these pathways are primarily parallel rather than integrated in the PVT. Ongoing work is using this method in combination with PavCA behavioral testing to determine whether these specific pathways are anatomically or functionally different in sign- versus goal-trackers.

Disclosures: S.S. Desrochers: None. **S.B. Flagel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.02/N22

Topic: G.03. Motivation

Support: Pritzker Neuropsychiatric Disorders Research Consortium
University of Michigan Undergraduate Research Opportunity Program

Title: Different outcome values influence the vigor of sign-tracking behavior in rats

Authors: R. LI[1], S. S. DESROCHERS[2], *S. B. FLAGEL[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Michigan Neurosci. Insitute, Univ. of Michigan, Ann Arbor, MI

Abstract: In our day-to-day lives, cues in the environment guide our behavior. Cues such as fast-food signs alert us to the availability of tasty food, often prompting us to stop to eat. Such cues can sometimes gain inordinate control over an individual's actions, leading to maladaptive behavior. For example, the sound of a slot machine or the sight of drug paraphernalia are cues that can elicit reward-seeking or relapse in individuals with a gambling problem or substance use disorder. We can model aspects of these behaviors in animals to better understand their neural components and underlying psychological processes. During a Pavlovian conditioned approach paradigm, wherein a discrete cue predicts a food reward, some rats, upon cue presentation preferentially interact with the reward delivery location (“goal-tracking”), whereas other rats exhibit an approach response that includes orienting towards and interacting with the cue itself (“sign-tracking”). Rats that exhibit this latter behavior, known as “sign-trackers”, attribute incentive motivational value to reward-associated cues and have a greater propensity for impulsive behavior, attentional deficits, and cue-induced drug-seeking behavior. However, it is not known if different outcome values affect the vigor of sign-tracking behavior. Here, we will explore how the value of reward associated with a cue affects the degree of responding. Specifically, a standard Pavlovian conditioned approach procedure consists of trials in which a lever-cue is presented for 8 seconds, and, upon its retraction, food reward is delivered in an adjacent food cup. In this experiment, conducted in adult male and female Sprague Dawley rats, two lever-cues are randomly presented one at a time with the lever-cue on one side of the

chamber predicting a large reward (3 pellets) and the lever-cue on the other side predicting a smaller reward (1 pellet). We found that sign-tracking behavior increases with reward size, with more interaction with the lever-cue associated with the large reward compared to that associated with the smaller reward. There was no effect on goal-tracking behavior, suggesting that sign-tracking is more sensitive to variations in outcome value. This study offers insights into identifying additional characteristics of sign-tracking behavior and will guide future work in understanding how cues associated with reward affect motivated behaviors relevant to psychiatric disorders such as substance use disorder.

Disclosures: R. Li: None. **S.S. Desrochers:** None. **S.B. Flagel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.03/N23

Topic: G.03. Motivation

Support: NIH Grant R01-DA054094

Title: The effects of semaglutide (Ozempic®) on the attribution of incentive motivational value to reward cues

Authors: *S. E. CHANG[1], S. B. FLAGEL[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Although initially designed for the treatment of type-2 diabetes, glucagon-like-peptide-1 (GLP-1) receptor agonist drugs such as Ozempic® have recently surged in popularity due to their ability to induce weight loss. Preclinical studies report that GLP-1 receptor agonists reduce food and alcohol intake, as well as opioid- and cocaine-seeking behavior. Similarly, anecdotal reports in humans suggest that GLP-1 agonists may generally diminish addiction-related behaviors. This led us to hypothesize that GLP-1 agonists affect the attribution of incentive salience to reward cues, a psychological process that promotes food- and drug-seeking behaviors.When rats are exposed to a Pavlovian conditioned approach paradigm wherein a lever-cue is followed by presentation of a food reward, some rats come to approach and interact with the lever-cue (sign-tracking), whereas others approach the site of food delivery (goal-tracking). While both sign-tracking and goal-tracking result from the attribution of predictive value to the lever-cue, sign-tracking reflects the additional attribution of incentive value.Here, male and female adult Sprague-Dawley rats were administered escalating doses of semaglutide (SEMA; 7-28 ug/kg, s.c.) or vehicle (VEH) over the course of 10 days and then maintained at the highest dose of SEMA (or VEH) for 5 daily Pavlovian conditioned approach sessions. This SEMA dosing regimen prevented significant weight gain (i.e., <10% gain) but did not result in robust weight loss (i.e., <5% loss). While both male and female rats treated with SEMA gained less

weight compared to those treated with VEH, the effect of SEMA on body weight was more pronounced in male rats. As there was variability in weight gain, SEMA rats were further divided into “high” and “low” SEMA responders based on change in weight. Relative to VEH rats, male rats with the least amount of weight gain (i.e., high SEMA-responders) had a greater tendency to sign-track; and those with the most weight gain (i.e., low SEMA-responders) showed higher levels of goal-tracking behavior. In agreement, the change in weight from baseline negatively correlated with the tendency to sign-track in male SEMA rats. There was not an effect of SEMA on sign- or goal-tracking behavior in female rats, and this may be related to the fact that females were less responsive to the effects of SEMA on body weight. Ongoing studies are assessing the effects of other SEMA dosing regimens on weight gain and incentive motivation in male and female rats. These data suggest that, at least in male rats, GLP-1 agonists affect the propensity to attribute incentive salience to reward cues.

Disclosures: S.E. Chang: None. **S.B. Flagel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.04/N24

Topic: G.03. Motivation

Support: NIH R01 DA038599
NIH T32-DA007281

Title: The neurochemical profile of the paraventricular nucleus of the thalamus in sign-tracker and goal-tracker rats

Authors: *B. A. RAMOS[1], R. KENNEDY[1], S. B. FLAGEL[2];
[1]Neurosci., [2]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Neurochemical imbalances are known to contribute to psychiatric disorders. To examine the neurochemical correlates that may render one more susceptible to mental illness, we use an animal model that allows us to capture a “neurobehavioral endophenotype” of relevance. When exposed to a Pavlovian conditioned approach (PavCA) paradigm consisting of lever-cue presentation followed by reward delivery, rats will learn the cue-reward relationship and attribute predictive value to the lever-cue, but a subset of rats, referred to as sign-trackers (STs), also attribute incentive value to the lever-cue. For STs, the lever-cue can control behavior in a maladaptive manner. Relative to goal-trackers (GTs), who primarily attribute predictive value to the lever-cue, STs are more impulsive, have attentional deficits, and show greater reinstatement of drug-seeking behavior. The behavior of STs is thought to result from dominance of subcortical systems, whereas that of GTs derives from engagement of cortical systems. The paraventricular nucleus of the thalamus (PVT) has emerged as a key neural node that may differentially integrate subcortical and cortical input in STs and GTs and, in turn, guide cue-

motivated behavior. Here, we utilized a liquid chromatography mass spectrometry (LC-MS) method paired with benzoyl chloride (BzCl) labeling to characterize the neurotransmitters, their metabolites, and energy molecules that contribute to the role of the PVT in encoding the value of reward cues and eliciting behavior. Specifically, we combined a neurochemical profiling approach with microdialysis in male and female rats to quantify a panel of 20 neurochemicals in the posterior PVT (pPVT). Sampling occurred prior to the 1st session of PavCA and the day after the last (5th) session of PavCA. Rats were characterized as STs, GTs, or intermediate rats (INs; i.e., those that vacillate between sign- and goal-tracking behavior) based on their PavCA behavior. Relative to GTs and INs, STs tend to exhibit an increase in the concentration of multiple neurochemicals from pre-PavCA (i.e., prior to learning the cue-reward relationship) to post-PavCA (i.e., after the behavioral phenotype is established). This pattern was most apparent with glutamate, aspartate, and vanillylmandelic acid (VMA) concentrations. Ongoing studies will determine if sex affects the neurochemical signature of the pPVT. This research will identify neurochemical markers that predispose an animal to a form of associative learning that promotes maladaptive behavior and may therefore be critical to the development of novel therapeutic targets for the treatment of psychiatric disorders.

Disclosures: B.A. Ramos: None. **R. Kennedy:** None. **S.B. Flagel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.05/N25

Topic: G.03. Motivation

Support: NIDA R21 DA052594
T32 DA7281

Title: Knockdown of the glucocorticoid receptor (GR) in a corticostriatal pathway increases the propensity to attribute incentive salience to a reward cue

Authors: *P. FELIX[1], S. E. CHANG[1], J. P. HERMAN[2], S. B. FLAGEL[3];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept Pharmacol. and Systems Physiol., Univ. of Cincinnati, Cincinnati, OH; [3]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Environmental stimuli, or cues, can guide our behavior in adaptive ways, bringing us closer to valuable resources, like food; but such cues can also elicit maladaptive and potentially psychopathological behavior. For example, individuals with substance use disorder (SUD), often relapse when they encounter a cue (e.g., paraphernalia) that was previously associated with drug use, and this occurs regardless of one’s desire to remain abstinent. Reward-associated cues come to control behavior when they are attributed with incentive motivational value and thereby transformed into powerful incentive stimuli. Only some individuals, however, are prone to attributing incentive value to reward-associated stimuli, and these individuals appear to generally

lack inhibitory control over their behavior. Here, we investigate the glucocorticoid receptor (GR) as a potential neuromolecular mechanism of inhibitory control using the propensity to attribute incentive value to reward-cues (i.e., to sign-track) as a behavioral outcome measure. GR has been implicated in multiple psychiatric disorders characterized by deficits in inhibitory control, including SUD and impulse control disorders. In the current experiment, we used transgenic Sprague-Dawley rats with conditional GR knockdown alleles to selectively knock down GR in a "top-down" inhibitory control pathway from the prelimbic cortex (PrL) to the nucleus accumbens core (NAcC). Glutamatergic projections from the PrL to the NAcC are known to modulate reward-seeking behavior and regulate NAcC dopamine (DA) activity; and GR also plays a role in reward-related behaviors and regulates NAcC DA. To assess the effects of GR knockdown on the attribution of incentive salience to a reward cue (i.e., sign-tracking), rats underwent 5 sessions of a Pavlovian conditioned approach (PavCA) paradigm consisting of the presentation of a lever-cue paired with delivery of food reward. We successfully and selectively knocked down the expression of GR in PrL neurons projecting to the NAcC in transgenic rats (fl/fl) relative to their wildtype counterparts (wt/wt). Rats (fl/fl) who received pathway specific GR knockdown were more likely to attribute incentive salience to the reward cue (i.e., to sign-track) relative to wt/wt rats. Further, the degree of GR knockdown correlated with the tendency to sign-track. There do not appear to be sex differences in these effects. These findings highlight a role for GR as a neurmolecular mechanism of inhibitory control within the corticostriatal pathway.

Disclosures: P. felix: None. **S.E. Chang:** None. **J.P. Herman:** None. **S.B. Flagel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.06/N26

Topic: G.03. Motivation

Support: NIH Grant R15DA058186

Title: The Relationship between Social Reward Behavior and Modes of Dopamine Release

Authors: *T. R. ERICKSON, H. E. FRANKS, M. J. AL AZZAWI, D. B. LESTER;
Univ. of Memphis, Memphis, TN

Abstract: Deficits in social behavior, such as a loss of motivation and social avoidance are key symptoms in several psychiatric disorders. The mesolimbic dopamine system, which consists of dopamine cell bodies in the ventral tegmental area (VTA) that project to limbic regions such as the nucleus accumbens (NAc), is thought to mediate reward seeking and motivation for reinforcing stimuli, including social interaction. Emerging evidence suggests that different modes of reward (such as drug vs social) may depend on different modes of dopamine release (phasic vs tonic, respectively). The current study investigated the relationship between behaviors

associated with social reward and NAc dopamine release elicited by phasic/tonic stimulation patterns in C57Bl/6J mice. Social conditioned place preference (sCPP) will be used to assess preference/aversion to chambers paired with social interaction. Increased time spent in the social paired chamber on day 10 minus day 1 indicates increased preference for social interaction. Following sCPP, we used in vivo fixed potential amperometry to measure VTA stimulation-evoked dopamine release in the NAc of anesthetized mice. To challenge this reward system during dopamine recordings, mice were administered an injection of cocaine (10 mg/kg, ip). The mice displayed a wide range of social preference scores, with no differences in social preference between male and female mice. Social reward behaviors did not significantly correlate with baseline (pre-cocaine) phasic or tonic dopamine release. In males, however, we observed a significant negative relationship between social preference and cocaine-induced changes in phasic dopamine release, meaning that increased motivation for social interaction was associated with a decreased dopaminergic response to cocaine. The female mice did not display a significant relationship between social preference and dopaminergic response to cocaine. These findings indicate potential differences in the way the mesolimbic dopamine system mediates social vs drug reward and that these differences may be sex dependent.

Disclosures: T.R. Erickson: None. **H.E. Franks:** None. **M.J. Al Azzawi:** None. **D.B. Lester:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.07/N27

Topic: G.03. Motivation

Support: NIH Grant R15DA058186

Title: Social Hierarchy and Mesolimbic Dopamine Release in Mice

Authors: T. R. ERICKSON, M. J. AL AZZAWI, S. C. LOWE, ***D. B. LESTER**;
Univ. of Memphis, Memphis, TN

Abstract: The mesolimbic dopamine system is involved in mediating reward processing, motivation, and reinforcement learning. Dysfunction within this system has been implicated in many psychiatric disorders, including addiction, ADHD, and depression. Both human and animal studies have demonstrated that social experiences can alter mesolimbic dopamine functioning; however, relatively few studies have examined the effects of social hierarchy on dopamine dynamics within this system. In this study, we used the social dominance tube task to characterize mice as either socially dominant or submissive, and then used in vivo fixed potential amperometry to measure dopamine release in the nucleus accumbens (NAc) of anesthetized mice in response to electrical stimulations set to mimic phasic or tonic firing patterns. Male and female C57Bl/6J mice were housed in same-sex pairs from weaning to adulthood, and testing

revealed clear dominance-submission relationships within the cages for both males and females. Social hierarchy altered mesolimbic dopamine dynamics in a sex dependent way. Socially dominant males did not differ from submissive males in phasic dopamine release or the dopaminergic response to cocaine. However, socially dominant males exhibited a greater concentration of dopamine release in response to tonic stimulations compared to submissive males. Socially submissive males displayed tonic dopamine release concentrations similar to those observed in female mice. In female mice, no significant differences were observed in baseline phasic or tonic dopamine release based on dominance or submission. However, socially submissive females exhibited an increased dopaminergic response to cocaine compared to dominant females. These findings suggest that social hierarchy has differential effects on dopamine dynamics in males and females. These neurochemical effects may relate to hierarchy-induced changes in behaviors associated with reward and motivation.

Disclosures: T.R. Erickson: None. **M.J. Al Azzawi:** None. **S.C. Lowe:** None. **D.B. Lester:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.08/N28

Topic: G.03. Motivation

Support: University of Minnesota MnDRIVE Initiative
NIH R01 MH129370-01

Title: Investigating the role of the parafascicular thalamus in cue-directed behavior

Authors: *L. C. KUPER[1], A. R. WOLFF[2], B. T. SAUNDERS[2];
[1]Neurosci., Univ. of Minnnesota, Minneapolis, MN; [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Cue reactivity acts as the foundation for attention, motivation and learning. Many neuropsychiatric disorders such as addiction, schizophrenia, and ADHD are diseases of inappropriate reactivity to cues in the environment. The parafascicular (PF) thalamus is well-placed as an integrative hub for cue processing. It receives direct inputs from the superior colliculus, an area involved in guiding attention to unexpected stimuli, and is known to be activated during behaviorally significant sensory events. The PF sends dense outputs throughout the striatum, including the dorsomedial striatum, dorsolateral striatum, and nucleus accumbens. These projections contact medium spiny neurons as well as cholinergic interneurons, which have recently emerged as a key local regular of striatal dopamine dynamics. Previous work has shown that the PF is necessary for shifts in attention and behavioral updating, likely via its striatal outputs. It is also involved in motor behaviors including orienting towards a stimulus. Little work has investigated the role of these thalamostriatal projections in visual cue-directed Pavlovian

associations. We recorded PF calcium activity in rats using fiber photometry during a cue-directed Pavlovian conditioning task, and analyzed their movement using deep learning. We found that PF neurons have distinct patterns of activity related to cue associations, motor activity, and reward. Global activation of the PF with optogenetics confirmed these dissociable roles. Activation caused ipsilateral turning and was generally rewarding. In ongoing studies, we are interrogating the role of PF projections specifically to the nucleus accumbens and dorsomedial striatum, to better understand how these subcircuits contribute to attentional shifting in Pavlovian versus versus operant learning.

Disclosures: L.C. Kuper: None. **A.R. Wolff:** None. **B.T. Saunders:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.09/N29

Topic: G.03. Motivation

Support: 1 R01 MH129370-01A1

Title: Examining Somatodendritic Dopamine Signaling in the VTA and SNc during Pavlovian Learning

Authors: *G. STEMMLER, A. R. WOLFF, B. T. SAUNDERS;
Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Dysregulation of brain reward networks that govern learning processes and motivated behavior is a key tenant of substance use disorders. Specifically, drugs of abuse and drug predictive stimuli act upon mesolimbic dopamine systems that are crucially involved in reward learning and in mediating reward directed behavior. The ventral tegmental area (VTA) and substantia nigra (SNc) are a major source of dopamine neurons that project throughout the brain and integrate sensory and emotional information to reinforce valenced learning, motivation, and invigoration. Notably, dopamine neurons in these regions are not only regulated by synaptic inputs, but through local dopamine release by both vesicular and non-canonical methods at somatic and dendritic regions. The in vivo temporal dynamics of somato-dendritic dopamine release during learning are largely unknown, a critical gap to unveiling the complexities of dopamine neuron function. In this study, we used fiber photometry with the dopamine fluorescent sensor, dLight1.3b, in the rat VTA/SNc to examine somato-dendritic dopamine signaling during Pavlovian learning. We first assessed the dopamine response to reward predictive cues, a tone, and rewarding stimuli itself, a sucrose delivery, to determine local dopamine signaling in the midbrain during appetitive conditioning. We then examined VTA dopamine responses during fear conditioning, where a cue was associated with aversive shock. Lastly, we employed dual color photometry to simultaneously monitor somato-dendritic dopamine signaling and dopamine neuron activity in the VTA. We were successfully able to

record dopamine dynamics in these midbrain regions and to identify changes in the local dopamine signal due to both rewarding and aversive stimuli. VTA somato-dendritic dopamine signals showed variable responses to reward consumption, while SNc dopamine signals increased during sucrose consumption. Notably, conditioned, cue-evoked somato-dendritic dopamine signaling was not apparent even after extended Pavlovian training. This was in contrast to dopamine neurons themselves, which were strongly activated by conditioned cues after learning. These results and further study will provide valuable insight into somatodendritic dopamine dynamics during learning and will have further implications in understanding the complex regulation of midbrain dopamine neurons during motivated behavior.

Disclosures: G. Stemmler: None. **A.R. Wolff:** None. **B.T. Saunders:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.10/N30

Topic: G.03. Motivation

Support: 5R01MH121350

Title: Investigating the neural mechanisms of effort-based behaviors: Effects of local response rate and tetrabenazine on theta local field potential recordings in prefrontal cortex, nucleus accumbens, and dorsal hippocampus.

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Abstract: The nucleus accumbens (NAc) plays a pivotal role in cognitive, motor, and motivational processes, including the exertion of effort in goal-directed behaviors. It receives diverse inputs, including glutamatergic and GABAergic connections from prefrontal cortex (PFC) and hippocampus (HPC). Task-dependent relationships between theta oscillations in the HPC, medial PFC, and NAc have been observed, highlighting their involvement in effortful behaviors. Considerable evidence shows that tetrabenazine (TBZ), a VMAT-2 inhibitor and dopamine-depleting agent, suppresses the exertion of effort in instrumental behavior and induces a low-effort bias in animals tested on choice tasks. We investigated the effects of TBZ on neural activity in the dorsal HPC (dHPC), PFC, and NAc in awake-behaving rats performing a high-effort lever pressing task for food reinforcement (fixed ratio (FR) 40 schedule). After FR40

training, male Sprague-Dawley rats were implanted bilaterally with sixteen 50-micron tungsten wires, including 2-channel wires in dHPC and PFC, and 4-channel wires bilaterally in NAc. Following recovery and retraining, rats received IP injections of 1.0 mg/kg TBZ and vehicle using a within-subject design. TBZ substantially reduced lever pressing on the FR40 schedule. Theta band was defined as 6-12 Hz, and linear mixed-effects modeling revealed that TBZ modestly but significantly decreased theta peak frequency and power. Theta peak power was most dominant in the dHPC and differed from both NAc and PFC. Analysis of two-second epochs based on the local rate of responding showed that both theta frequency and power were highest when there were no lever presses, and decreased as lever pressing rates increased, with a more pronounced effect in the dHPC. TBZ further affected theta peak power and frequency in relation to lever pressing rate, indicating its modulatory effect on neural dynamics during exertion of effort. These findings deepen our understanding of the neural mechanisms underlying effort-based behaviors and the impact of TBZ in rat models of effort-related motivational dysfunction.

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Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.11/N31

Topic: G.03. Motivation

Support: NIMH grant 5R01MH121350 granted to JDS

Title: Spectral analysis of local field potentials during instrumental behavior and with dopamine depletion

Authors: *A. MANKILI[1,2], A. ECEVITOGLU[1,2], N. REN[1], R. A. ROTOLO[1], I. H. STEVENSON[1,3,2], J. J. CHROBAK[1,2], J. D. SALAMONE[1,2];
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Abstract: Dopamine plays a major role in motivated behavior, and dopamine transmission is involved in a variety of motivational dysfunctions such as psychomotor retardation, anergia, fatigue, and apathy. In this study, we used low doses of the VMAT-2 inhibitor tetrabenazine (TBZ) to induce depressive-like motivational dysfunction in male rats. We then recorded Local Field Potentials (LFPs), bilaterally from Hippocampus, Nucleus Accumbens and Prefrontal Cortex in rats injected with TBZ or Vehicle (VEH), using chronically implanted electrode drives while the animals performed an effort-based lever pressing task (a high-effort fixed ratio 40 task). We analyzed the LFP data, focusing on how spectra change during different phases of

lever pressing behavior. We found that both theta band power and peak frequency decrease with local press rate, and there was a small but significant effect of TBZ treatment. More generally, we find changes in delta, theta, and gamma power at the onset of lever pressing and over the course of ratios, as well as changes in coherence across brain areas and hemispheres. We modeled the lever pressing behavior of the animals by using a Poisson generalized linear model (GLM) and fitting rate of lever pressing using the LFP amplitude in different frequency bands, as well as, peak frequency in the theta band. We found that, when fit to individual animals, the models explain approximately 40% of the variance in pressing behavior on average. These distributed patterns of LFP variation may be potential biomarkers for motivation and motivational dysfunction.

Disclosures: A. Mankili: None. **A. Ecevitoglu:** None. **N. Ren:** None. **R.A. Rotolo:** None. **I.H. Stevenson:** None. **J.J. Chrobak:** None. **J.D. Salamone:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.12/N32

Topic: G.03. Motivation

Title: Ratiometric detection of wideband dopamine fluctuations in the striatum

Authors: *A. GOTTSCHALK[1], A. HAMID[2];
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Abstract: Reward learning, cognition, and motivation are supported by fluctuations in brain dopamine levels over multiple timescales. Recent efforts to develop methods to quantify dopamine changes do not effectively bridge timescales of dopamine variation, limiting the ability to interrogate the relationship between fast-phasic and slow-tonic changes in dopamine. Here, we sought to overcome these limitations by enhancing standard fast-scan cyclic voltammetric approaches for dopamine measurement to quantify broadband dopamine changes across timescales. Our method relies on varying the adsorption epoch of successive redox ramps to rapidly modify the sensitivity of the carbon fiber to dopamine. This allowed us to counteract electrode drift by subtracting unstable faradaic currents for each sample, thus reporting subsecond dopamine changes over many hours. We extensively validate our strategy in flow cell systems and in vivo, with pharmacological and optogenetic manipulation of dopamine with simultaneous microdialysis. Our approach provides a robust platform to assess the contributions of multi-timescale, wideband dopamine changes to cognition, movement, and motivation.

Disclosures: A. Gottschalk: None. **A. Hamid:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.13/N33

Topic: G.03. Motivation

Support: NIH Grant NS083059

Title: The Impact of GPR6-KO on Cost-Benefit Learning and Striatal Dopamine Transmission

Authors: *F. BONNESON[1], A. HAMID[2];
[1]Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Differential learning from gains and losses across reward rates is a feature of flexible behavioral learning. Current reinforcement learning theories posit that learning from gains and losses is facilitated by parallel basal ganglia pathways, with the D1 circuit specialized for benefits and the D2 circuit specialized for risk. While previous studies have investigated brain circuits that facilitate behavioral flexibility by regulating learning and motivation, details about their interactions and sensitivity to tonic and phasic dopamine remain unknown. Here, we set out to understand how learning about costs (learning from losses) and benefits (learning from gains) are supported by opponent basal ganglia pathways. D2 dopamine receptors in striatal medium spiny neurons accumulate evidence for costs and restrain behaviors, a process critically refined by dopamine. The intracellular cascade initiated by the D2 receptor interacts with an orphan G-protein coupled receptor 6 (GPR6), with unknown cellular function and behavioral consequence. We utilized mice lacking GPR6 (GPR6-KO mice) to study how learning from costs within the D2 pathway affects behavior. We used a two-lever probabilistic trial and error task where mice had to dynamically adjust their choices to changing reward probabilities. Our preliminary results indicate that wild-type mice will adjust their behavior in response to gains and losses. We have extended this analysis to heterozygous and homozygous GPR6-KO mice and their littermate controls. Moreover, we have initiated simultaneous measurement of spectrally separated striatal dopamine and acetylcholine during the decision-making of wild-type and GPR6-KO mice. Together, this project will summarize our progress in characterizing the selectively D2-MSN enriched GPR6 protein through cost-benefit learning.

Disclosures: F. Bonneson: None. **A. Hamid:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.14/N34

Topic: G.03. Motivation

Support: HHMI Gray Fellowship to AAH

Title: Is spatiotemporal coordination of DA across caudate-putamen relevant for psychosis?

Authors: *D. FLINK[1], A. GAMAM[1], A. HAMID[2];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Deficits in representing and learning about states of the world underlie hallmarks of maladaptive cognitive control and reward learning in psychosis. The neurotransmitter dopamine (DA) and frontostriatal interactions are critical to adaptively regulating these processes in service of behavioral flexibility. Despite decades of research, our understanding of the precise computational and circuit-level mechanisms underlying psychosis—particularly the role of DA activity across spatial and temporal scales —remains incomplete. Here, we set out to test the hypothesis that spatiotemporal DA coordination in the dorsal striatum may serve key computations in service of state estimation and learning during flexible decision-making, and their disruption may relate to failure modes in psychosis. This hypothesis is inspired by the observation that tightly coordinated DA activity patterns organized into wave-like dynamics codify the relative timing of DA prediction error signals between the caudate and putamen nuclei. Moreover, features of spatiotemporal DA wave dynamics were sensitive to behavioral demands that required mice to estimate task states predictive of rewards, especially the accumulation of evidence for agentic control. We provide results from experiments that test how DA wave features, including propagation directionality, latency, locus of origin, and stimulus-response, are affected by pharmacological and genetic psychomimetic conditions. By relating these findings to DA wave parameter changes in mice learning probabilistic reversal tasks, we aim to link how hyperdopaminergia (and psychotropic medications) regulates DA substrates for computing reward contingency and agentic control.

Disclosures: D. Flink: None. **A. Gamam:** None. **A. Hamid:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.15/N35

Topic: G.03. Motivation

Support: HHMI Hanna Gray Fellowship to AAH

Title: Assessing Striatal Dopamine-Acetylcholine Interactions During Cue-Reward Learning and Pharmacological Intervention

Authors: *A. M. GAMAM[1], H. WEHELIE[2], D. FLINK[1], A. HAMID[3];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Virginia Sch. of Med., Charlottesville, VA; [3]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Reward-evoked striatal dopamine release displays a wave-like pattern influenced by task demands, challenging current hypotheses of widespread midbrain synchronization. Understanding these dynamics requires a deeper understanding of mechanisms that regulate striatal DA release across spatial territories and temporal epochs. Previous studies have documented reciprocal regulatory interaction between striatal cholinergic interneurons and dopamine release, exhibiting wave-like dynamics. We simultaneously recorded dopamine and acetylcholine responses during Pavlovian cue-reward tasks to explore how spatial and temporal dopamine patterns impact dorsal striatum reward-credit learning. Our findings revealed dynamic changes in cue-induced and reward-induced responses in specific striatal regions. We supplement our findings under behavioral investigation with experiments that assess how dopaminergic, cholinergic, and psychomimetic pharmacological manipulations influence spatiotemporal dopamine-acetylcholine interactions.

Disclosures: A.M. Gamam: None. **H. Wehelie:** None. **D. Flink:** None. **A. Hamid:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

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Program #/Poster #: PSTR477.16/N36

Topic: G.03. Motivation

Title: Diet-induced changes in neurotensin signaling shape hedonic feeding and obesity progression

Authors: *N. GAZIT SHIMONI[1], A. TOSE[2], Y. JIN[4], J. VERHAREN[5], C. LIU[6], T. LUKACSOVICH[7], B. LIM[9], L. TIAN[10], C. FOLDY[8], S. LAMMEL[3];
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Abstract: The neuropeptide neurotensin (NTS) and its receptors are widely expressed and regulate many functions in the mammalian brain including sleep, feeding, blood pressure, body temperature and locomotion. We combined patch-seq, in-vivo and ex-vivo electrophysiology with opto-tagging, optogenetics and imaging to study the role of NTS in ventral tegmental area (VTA)→projecting nucleus accumbens lateral shell (NAcLat→VTA) neurons. This projection

represents a key circuit node of the brain's reward system (Yang et al., 2018; *Neuron)*, but the function of NTS in this pathway is unknown. We found that NTS is highly expressed and released during activation of NAcLat→VTA. In addition, we found that neural activity of NAcLat→VTA cells is directly correlated with consumption of palatable food but not regular chow or other behaviors. Accordingly, activation of NAcLat→VTA selectively promoted hedonic feeding in sated mice, in a NTS dependent manner. Intriguingly, in the high fat diet (HFD) obesity mouse model, we found a diet dependent uncoupling between NAcLat→VTA and hedonic feeding. This was accompanied by reduced NTS expression and release in HFD mice. Lastly, when we selectively overexpressed NTS in the NAcLat→VTA pathway of mice exposed to HFD, we observed a significant reduction in weight gain compared to control mice. Together, these data reveal an unexpected role for NTS in the NAcLat→VTA pathway for promoting hedonic feeding behavior, which is dependent on food environment. These findings contrast the well-known anorexic effects of NTS in the lateral hypothalamus suggesting that circuit-specific manipulations of NTS neurons are critical in order to harness the translational potential of NTS in the treatment of obesity.

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Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Topic: G.03. Motivation

Support: NIH Grant R01DA042889
NIH Grant F32MH127792

Title: Striatal acetylcholine and dopamine comprise spatially heterogeneous channels for reward and aversion encoding

Authors: *K. FRASER[1], J. READ[2], T. R. LA[2], Y. WU[2], J. W. DE JONG[2], S. LAMMEL[2]; [1]Univ. of California, Berkeley, Berkeley, CA; [2]Mol. and Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: It is now well-appreciated that dopamine neurons projecting to, and dopamine release within, distinct striatal subregions is highly heterogeneous in form and function. In contrast, striatal acetylcholine is generally presumed to be homogeneous - pausing to facilitate dopamine-mediated plasticity in the absence of encoding of valence, reward expectation, or the value of stimuli. We wondered if potential heterogeneity in striatal acetylcholine may have been overlooked as most studies of striatal acetylcholine have focused exclusively on the dorsal lateral striatum in rodents or putamen in non-human primates. To test this, we made use of fiber

photometry to simultaneously recorded dopamine and acetylcholine release in male and female C57BL/6J mice (n=28) across the striatum using the genetically modified biosensors GRAB-gACh4h and GRAB-rDA3m. We found that, at rest, as has been demonstrated for dopamine, that there are heterogeneous timescales for acetylcholine release across the striatum. We then trained mice on a probabilistic Pavlovian conditioning task where 3 different auditory cues were each associated with 100%, 50%, or 0% chance of reward delivery. To our surprise, we found a medial to lateral gradient within the nucleus accumbens for acetylcholine release to encode the expected value of reward-paired cues as well as reward-prediction error. We then tested whether these dynamics during reward processing held true for processing aversive events. Indeed, while the directionality of dopamine and acetylcholine release are altered depending on the valence of the received outcome, the general relationship between acetylcholine and dopamine release was preserved. Finally, we performed rabies-assisted monosynaptic tracing and observed distinct inputs to striatal acetylcholinergic neurons within the medial and lateral nucleus accumbens suggestive of a distributed circuit-based organization for control of striatal acetylcholine release. Taken together our results reveal a novel source of heterogeneity in the striatum for reward and aversion encoding that is driven by local acetylcholine release which ultimately opens new directions to understanding the striatal mosaic in motivated behavior.

Disclosures: K. Fraser: None. **J. Read:** None. **T.R. La:** None. **Y. Wu:** None. **J.W. De Jong:** None. **S. Lammel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.18/N38

Topic: G.03. Motivation

Support: Philanthropy (anonymous)

Title: A multi-institutional investigation of psilocybin's effects on mouse behavior

Authors: *O. D. LU[1], K. WHITE[1], K. RAYMOND[3], A. S. KLEIN[5], C. LIU[5], N. GREEN[6,5], S. VAILLANCOURT[3], A. GALLAGHER[5], A. LI[5], L. SHINDY[5], R. LI[2], M. ZOU[2], V. FAYNER[2], D. MIKULEK[2], A. B. CASEY[4], L. CAMERON[3], M. B. POMRENZE[3], J. DE JONG[1], H. ADESNIK[1], V. S. SOHAL[5], M. KHEIRBEK[5], A. M. GOMEZ[2,1], S. LAMMEL[1], B. D. HEIFETS[4], R. C. MALENKA[3];
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Abstract: Reproducibility issues are a major problem for science. It is too often the case that high-impact scientific publications turn out to be irreproducible, ultimately imposing a major

setback to the field, causing confusion, and wasting time, money, and resources. For rapidly growing fields, such as the field of psychedelic science, we have the opportunity to change the trajectory of scientific discovery in a way that maximizes true advancement - that is, by focusing on reproducibility early on. For the first time in decades, many investigators are obtaining access to and studying psychedelic drugs, and already, there are numerous publications suggesting that these drugs have astounding therapeutic potential for many different neuropsychiatric disorders. While these results are enticing, their reproducibility across labs is unknown. Here, we aim to comprehensively define the robust and reproducible behavioral effects of psilocybin. To accomplish this, we have taken a multi-institutional collaborative approach, where six labs are performing the same experiments to test the acute and persistent effects of a single 2 mg/kg dose of psilocybin on mouse behavior. So far, we have studied psilocybin's effects on a wide range of well-established mouse behaviors, including 1) anxiety-like behaviors in the open field test and elevated plus maze, 2) depression-like behaviors in the tail suspension and forced swim tests, 3) cognitive effects in novel object recognition and fear conditioning experiments, 4) exploration in the novel object exploration test, and 5) social behaviors in the 3-chamber social interaction test. Here, we find that a single dose of psilocybin has several robust and reproducible acute effects on mouse behavior, including increased anxiety-like behaviors and decreased exploration of a novel object. However, perhaps surprisingly, we find no clear and consistent effects 24 hours after drug administration, which conflicts with the widespread idea that psychedelics induce profound, long-lasting changes to behavior. Overall, our results both support the efficacy of our collaborative approach in identifying reproducible effects and highlight the necessity of reproducing findings before publication.

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Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.19/N39

Topic: G.03. Motivation

Title: Spatial and Temporal Dynamics of Mesolimbic Dopamine Signaling in Motivated Behavior.

Authors: *J. W. DE JONG, **Y. LIANG**, H. WANG, S. LAMMEL;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Ventral tegmental area (VTA) DA neurons are often thought to uniformly encode temporal-difference (TD) reward prediction error (RPE). However, recent studies have demonstrated a much greater diversity of DA function than previously assumed. There is increasing evidence that distinct VTA DA projections into different subregions of the nucleus accumbens (NAc), the prominent projections target of VTA DA neurons, mediate diverse behavioral functions (de Jong et al., 2019; Neuron). Additionally, our recent study identified a subgroup of DA neurons in the medial VTA that encodes a value-like signal while another subpopulation of DA neurons in the lateral VTA encodes the derivative of this value (de Jong et al., 2024; Nature Neuroscience). To further study the different anatomical and functional characteristics of DA subsystems in reward seeking behavior, we established a novel virtual reality task that enables flexible within-trial manipulations of key aspects of reward-seeking behavior. This task consists of an abstract visual cue that indicates the virtual distance to a reward. In the task, mice run on a wheel in order to move an abstract cue (i.e., a horizontal bar) to the target zone and receive a sucrose reward. We conducted in vivo fiber photometry recordings of DA release in different NAc subregions and found that there was a ramping increase of DA release in the medial NAc when mice approached the reward, and a transient increase of DA release in the lateral NAc at trial onset and reward delivery. Importantly, we found that DA release in the medial NAc depends on both the distance to reward and the running speed of the mice suggesting that it encodes the trial outcome discounted by the time it will take to obtain the reward (i.e. the distance divided by the running speed). Next, we leveraged Neuropixels electrode arrays in combination with fiber photometry to simultaneously measure local DA release and NAc single neuron activity in mice performing the behavioral task. We found that medial NAc single units primarily encode running speed instead of trial outcome. These findings emphasize the importance of considering the heterogeneity of DA neuron function in understanding the neural circuits underlying reward and motivation. Moreover, the combination of simultaneous high-resolution measurements using Neuropixels and fiber photometry offers a powerful approach to dissect how the NAc integrates multiple information streams to mediate motivated behavior.

Disclosures: J.W. De Jong: None. **Y. Liang:** None. **H. Wang:** None. **S. Lammel:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Title: Comparative neurotransmitter receptor architecture of the basal ganglia

Authors: *S. HEILBRONNER[1], R. B. MARS[2], K. BIJANKI[1], W. TANG[3], N. PALOMERO-GALLAGHER[4];
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Abstract: The densities of various neurotransmitter receptors can vary substantially across brain regions. Receptor architecture can be used to map regions, to understand the functional input-output relationships within and across regions, and even to establish homologous regions across species. To achieve these goals, receptor architecture must be mapped across a large number of receptors, in a manner consistent across regions and species. Although such experiments have been performed for many regions of the cerebral cortex, the same cannot be said of the basal ganglia. Thus, here, we performed receptor autoradiography and analyzed the densities of 15 receptors (AMPA, kainate, GABAA, GABAB, benzodiazepine, M1, M2, M3, noradrenaline, α1, α2, 5-HT1A, 5-HT2, D1, and D2) across different regions of the basal ganglia in humans, macaques, and rats. In the same subjects, we were able to assess receptor density across the cerebral cortex.
Receptor densities varied both across and within basal ganglia nuclei. For example, in all three species, some receptors showed patchy organization within the striatum, reflecting striosome-matrix organization. Nearly all receptor densities were notably higher in the striatum than in the globus pallidus, likely reflecting the reduced density of synapses in the latter.
We were also interested in the degree to which neurotransmitter receptor distribution was similar or divergent across species. Correlations in receptor densities between matched regions (e.g. rat pallidum-human pallidum) were all positive and significant. However, cross-region correlations were also positive, and several were significant. Still, in our preliminary analyses, the matched regional comparisons had higher correlation coefficients (mean r=0.72) than the unmatched ones (mean r=.46), $t(13)=3.32$, $p=0.006$. This points to shared receptor architecture in the basal ganglia across species, but does not rule out subtler species differences in specific receptor distributions.
Finally, consistent with prior literature, there were striking differences in receptor architecture between the basal ganglia and the cerebral cortex. These included low 5-HT1A serotonin receptor densities and high D1 receptor densities in the striatum relative to the cerebral cortex. Interestingly, generally higher cholinergic receptor densities were found in the putamen and caudate nucleus than in the cortex, and the opposite holds for GABA and glutamate receptors. Together, these findings demonstrate the utility of neural receptor mapping in subcortical structures across species.

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Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

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Program #/Poster #: PSTR477.21/N40

Topic: G.03. Motivation

Title: Disrupting microbiota composition and microbiota-gut-brain signalling: impacts on motivation

Authors: *B. L. SHARVIN[1,2], G. S. S. TOFANI[1,2], C. G. MCNAMARA[2], J. F. CRYAN[1,2]; [1]Anat. and Neurosci., [2]APC Microbiome Ireland, Univ. Col. Cork, Cork, Ireland

Abstract: Motivation and reward seeking is a fundamental element of survival. Motivational drive is modulated via an integration of internal biological and external environmental conditions. Interestingly, the last decade of research has unveiled a role for the microorganisms in our gut, collectively termed the gut microbiota, in regulating our mood and behavior. This biological phenomenon has been coined the microbiota-gut-brain axis. Thus, what role could these microorganisms play in influencing motivational drive and hedonic neurocircuitry via the microbiota-gut-brain axis? To address this question, we exposed adult male C57/BL6 mice to an antibiotic cocktail via the drinking water, to deplete the gut microbiota. Following this, we restricted their food intake and trained them on an operant conditioning paradigm to nose poke for a sucrose pellet. The training protocol consisted of a magazine training schedule, and fixed ratio 1, 3, and 6 before a final progressive ratio whereby the breakpoint for a sucrose pellet was assessed. The breakpoint is often considered a metric for motivation as it indicates the maximum number of nose pokes at which the animal reaches a point of discontinuation to engage with the task. Interestingly, we found that removal of the microbiome increased the amount of nose pokes and subsequent pellets earned across fixed ratio 1, 3, and 6 and the progressive ratio breakpoint, when compared to mice with a stable microbiome that received regular drinking water. This implies that an absence of microbial signals increases the motivation for a palatable reward. In addition, we wanted to assess in a separate cohort if re-shaping of the microbiome, post training and breakpoint measurements: (a) recovered normal breakpoint levels in an antibiotic washout group, and (b) increased motivation in a control group that then received antibiotics. Our preliminary data suggests a trend in gradual patterns of altered motivation that correlate with gut microbiota integrity. Overall, these results suggest that an absence of the gut microbiota increases motivation for a food reward. This provides evidence that dynamic changes in gut microbiota composition and microbial signals may influence reward neurocircuitry and subsequent effort-based reward-seeking behavior.

Disclosures: B.L. Sharvin: None. **G.S.S. Tofani:** None. **C.G. McNamara:** None. **J.F. Cryan:** None.

Poster

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Title: Multiple timescale dopamine signals coordinate motivation for reward

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Abstract: Midbrain dopamine neurons are thought to be involved in various brain functions, including motivation and learning. Previous studies have revealed diversities in dopamine signaling across multiple timescales. Understanding how our brains utilize these signals to predict values and coordinate motivated behaviors over varying timescales remains a hot topic. In this study, we recorded from optogenetically identified dopamine neurons in the ventral tegmental area while rats engaged in a self-paced, reward-based decision-making task. The aim was to characterize the activity of individual dopamine neurons in motivated behaviors across various timescales, including within a trial, across trials, and across blocks. First, we explored the diversity of temporal dynamics in dopamine neurons' reward prediction errors in response to sequentially delivered rewards, where the number and timing of rewards (thus, the magnitudes and timing of reward predictions) varied based on the animals' choices and the type of reward blocks (BIG and SMALL). Second, we examined how these temporal dynamics correlate with the timescales of dopamine signals necessary to obtain rewards at the end of trials. We found that dopamine neurons exhibited diverse temporal dynamics in response to sequentially delivered rewards. Several characteristics of individual dopamine neuron activities suggest that this diversity reflects the rate at which individual dopamine neurons discount values. These dynamics correlated with dopamine ramping activities toward task events, determining the timescales of individual trials. These dopamine signals varied from cell to cell and showed biased transmission to different projection targets. Our findings underscore the importance of timescales of dopamine signals in coordinating motivated behaviors toward rewards.

Disclosures: H. Matsumoto: None. **K. Mizuseki:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.23/O2

Topic: G.02. Reward and Appetitive Learning and Memory

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

Title: High test-retest reliability of nucleus accumbens activity during reward anticipation

Authors: *N. A. BOUTON, E. H. ELLIS, J. K. LEONG;
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Abstract: Recent research has questioned the reliability of Functional Magnetic Resonance Imaging (FMRI). Previous findings suggest poor test-retest reliability of FMRI measures across brain areas and tasks, and specifically in subcortical brain areas during reward-related tasks. Further, data from the Adolescent Brain Cognitive Development study showed low reliability and low stability of the fitted coefficients from whole-brain analyses of the Monetary Incentive Delay (MID) task. However, optimizing methods might improve reliability, for example: (1) acquiring single-band rather than multi-band FMRI sequences, (2) extracting raw activity rather than fitted coefficients, and (3) honing analyses to target brain areas during specific trial phases. To test this possibility, we collected data from 19 healthy adults (mean age = 28, 9 female). Each participant completed 80 trials of the MID task, repeated at 2 sessions 3 days apart. The task included only the large gain (+$5), large loss (-$5), and neutral ($0) conditions. We extracted raw percent signal change from the NAcc, which we defined as 8-mm diameter spheres (centered at Talairach coordinates +/- 10, 12, -1), and was registered from template-to-native space by aligning with each participant's T1 anatomical scan using Advanced Normalization Tools (ANTs). Our results first replicate the literature by demonstrating increased NAcc activity during anticipation of large gains than neutral rewards at both timepoints ($t(158) = 3.67$, $p < 0.01$). Critically, we achieved high reliability in the NAcc during gain anticipation ($ICC(3,1) = 0.88$, $p < 0.01$). Reliability of NAcc activity was highest during the large gain condition (+$5) and the anticipation trial phase. Our findings show that optimizing acquisition and analysis can lead to reliable measurement of subcortical brain areas during reward tasks.

Disclosures: N.A. Bouton: None. **E.H. Ellis:** None. **J.K. Leong:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.24/O3

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS082650

Title: Dopamine depletion-induced connectivity changes to direct and indirect pathway striatal projection neurons and their role in motor function

Authors: R. P. SEAL, J. C. BRAGUE, G. P. SINHA, D. A. HENRY, D. HEADRICK, ***B. M. HOOKS**;
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Abstract: The cardinal symptoms of Parkinson's Disease (PD) cause debilitating loss of motor function with poor treatment options. Motor symptoms are triggered by the loss of nigrostriatal dopamine, which causes changes in intrinsic excitability and extrinsic connectivity of striatal projection neurons (SPNs). In standard models, this shifts the balance of functional output from direct pathway D1 receptor-expressing SPNs to the indirect pathway D2 receptor expressing SPNs. Here, we show using two different experimental mouse models that a transient daily increase in striatal dopamine preserves mature spines and dendritic arbors specifically on direct pathway SPNs and results in normal contralateral paw reaching despite the depletion of striatal dopamine. The cortex and thalamus are the major sources of excitatory input to the striatum. Using cell-type specific driver mice and stereotaxic injections to express channelrhodopsins and fluorophores, we functionally and anatomically assessed changes in corticostriatal and thalamostriatal connectivity. Patch clamp recordings demonstrate that, following striatal dopamine depletion, corticostriatal input from two major populations of motor cortex cell types to dSPNs are lost in control mice and in models with transient dopamine elevation. Thalamostriatal inputs to direct and indirect SPNs are evaluated using comparable methods. Our data highlight the loss and preservation of specific connections to direct pathway SPNs as a novel potential strategy to treat the motor symptoms of Parkinson's Disease.

Disclosures: R.P. Seal: None. **J.C. Brague:** None. **G.P. Sinha:** None. **D.A. Henry:** None. **D. Headrick:** None. **B.M. Hooks:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.25/O4

Topic: B.04. Synaptic Transmission

Title: Computational exploration leading to incremental calcium currents across up-states in dendritic spines of biophysically detailed striatal neurons

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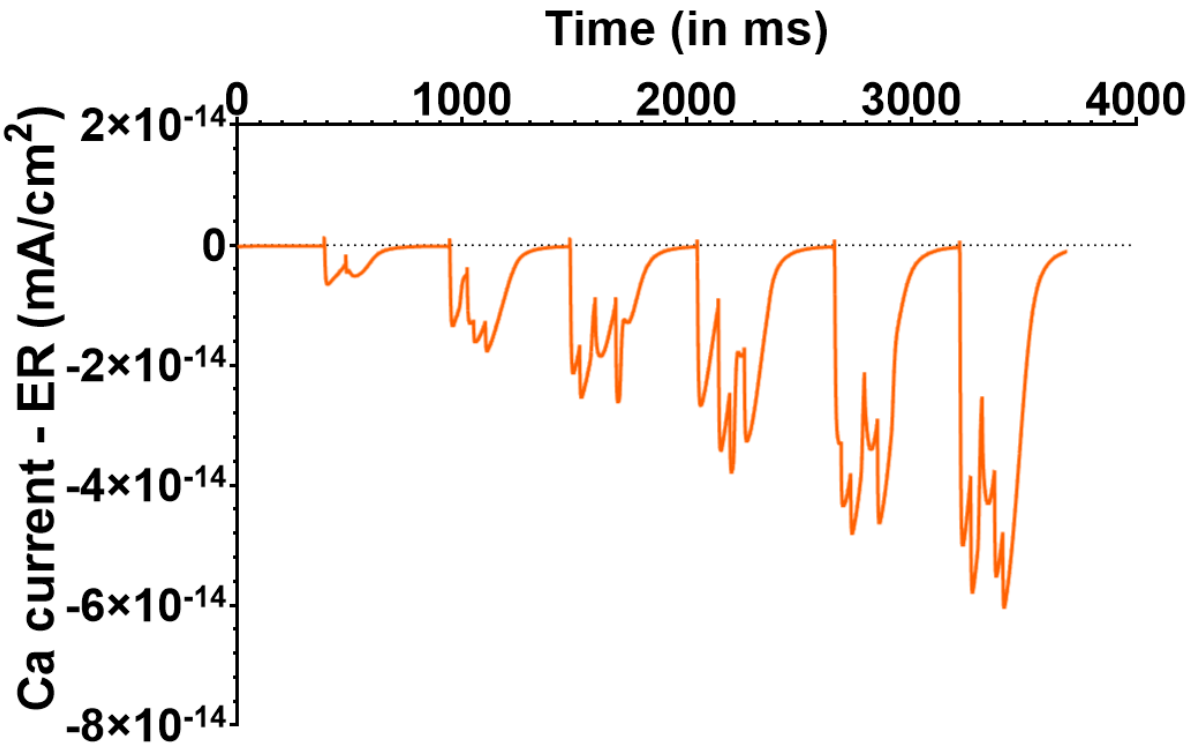
Abstract: In the dendritic spines of striatal medium spiny neurons (MSN), calcium concentration in the intracellular space is crucial in driving synaptic plasticity. The dynamics of calcium here originates via glutamate receptors, voltage-gated calcium channels, and intracellular calcium stores. In our model, two concentration pools of calcium - 'pool 1' that

affects the activity of calcium-sensitive potassium channels (BKKCa and SKKCa) and 'pool 2' affected by the activity of AMPA and NMDA receptors, were used. Evidence suggests that calcium from intracellular stores such as Endoplasmic Reticulum (ER) act on BKKCa and SKKCa channels, therefore, they interact with pool 1. Furthermore, voltage gated Ca^{+2} channels - CaR, CaQ and CaN contribute to the pool 1 whereas voltage-gated Ca^{+2} channels - CaL1.2, CaL1.3 and CaT contribute to pool 2. The ER was modelled to constitute fluxes through IP3 and ryanodine receptors. The dendritic spine, our region of focus, is part of a larger biophysically detailed MSN model that is receiving synaptic input drive varying across alternating down-states and up-states. As shown in figure 1, when the calcium currents of ER were recorded during simulations of the MSN model, it was found that the magnitude of calcium current increased with every consecutive up-state. The negative sign indicates calcium release from ER to intracellular space of dendritic spine. This dynamic was observed in absence of synaptic inputs (except dopamine) on this dendritic spine; however, nearby spines received synaptic inputs. The synaptic frequency on nearby spines was maintained across up-states. The increment of calcium currents across up-states is occurring even after being interspaced by low activity down-states, indicating a memory of the previous up-state carried forward. When calcium and dopamine signaling occur in absence of glutamate input, the spine could undergoes structural loss and/or long-term depression (LTD) of its synapses. Therefore, the incremental calcium potentially signals the cell to lose the spine or could be triggering molecular cascades that are unexplored.



Disclosures: N. Anisetty: None. **R. Manchanda:** None.

Poster

PSTR477: Decision Making: Circuit and Molecular Mechanisms

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR477.26/O5

Topic: G.03. Motivation

Support: Quinnipiac University QUIP-RS Summer Fellowship
Quinnipiac University College of Arts and Sciences Grant-in-Aid funding

Title: Sex differences in maternally separated rats on different effort-related decision making tasks

Authors: *J. N. MILLER[1], T. M. PANTALENA[1], J. R. MATHEWS[2], H. G. VAN BLARCOM[3], E. METJAHIC[1], A. J. BETZ[1], J. L. HAIGHT[1];
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Abstract: Maternal separation (MS) is an early life stressor used to model early life adversity. MS-induced depression-like behavior is commonly assessed in rodents with the forced swim test, which is thought to measure behavioral despair. Amotivation, another symptom associated with depression and other psychiatric illnesses like schizophrenia, is described as a lack of appetitive effort and is not accurately modeled with the forced swim test. Thus, the degree to which reward-seeking motivational behavior is impacted by MS is not known. Male and female rats underwent MS and were then tested in two effort-related choice tasks to assess amotivation-like behavior; one involving lever pressing (FR5 task) and one involving barrier climbing at differing heights (barrier task). Both required rats to choose between exerting effort to obtain a desirable reward or consuming freely available, standard laboratory food. Results from the FR5 task show that in adolescence, male and female rats that experienced MS pressed the lever less than control rats, indicative of an amotivational-like phenotype. Testing has been ongoing through adulthood, and sex differences in the lasting effects of MS on behavior are being observed, with male rats showing long-lasting deficits in lever-pressing behavior. Analysis of data from the barrier task is currently ongoing. Preliminary results suggest that a sex difference may be observed across tasks, with MS males showing a decrease in effort on both tasks and females only showing decreased effort on the FR5 task. In addition to finalizing the data analysis for the barrier task, next steps include assessing the effects of a second stressor on effort-choice behavior in MS and control rats in the FR5 paradigm.

Disclosures: J.N. Miller: None. **T.M. Pantalena:** None. **J.R. Mathews:** None. **H.G. Van Blarcom:** None. **E. Metjahic:** None. **A.J. Betz:** None. **J.L. Haight:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.01/O6

Topic: G.03. Motivation

Support: The Hilda and Preston Davis Foundation Award Programs in Eating Disorders Research

Title: Food biases and emotional arousal alter reward learning in typical and disordered eaters

Authors: *N. ROUHANI[1], C. GROSSMAN[2], J. D. FEUSNER[3], A. TUSCHE[4];
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Abstract: The urge to eat engages primary reward systems in the brain, thought to bias preference for energy-dense or high-calorie food more likely to sate hunger. Yet, this notion doesn't hold for individuals struggling with symptoms of eating disorders where high-calorie food is avoided. We developed a novel paradigm to investigate whether and how biases for high- and low-calorie food alter reward learning and decision-making in a large sample of participants with typical or disordered eating behavior. Importantly, food characteristics (high- versus low-calorie) were incidental to the task goal of maximizing monetary reward. Using an emotional arousal manipulation, we also examined whether heightened arousal, thought to influence goal-directed behavior, enhanced the impact of food biases on reward learning. Consistent with prior notions of food-relevant biases, we found and replicated that the typical-eating group learned better when *high*-calorie foods were more rewarding, while the disordered-eating group learned better when *low*-calorie foods were more rewarding. The arousal manipulation enhanced this group-dependent bias. Fitting behavior to reinforcement learning models enabled us to identify distinct cognitive components underlying the effect of food biases on learning and decision-making: Typical and disordered eaters showed differences in their pre-experimental preference for a food type (high- or low-calorie food, respectively) and the extent to which they learned from positive outcomes associated with that preference. These findings provide a mechanistic account of *how* food biases alter reward-based choice, especially under heightened arousal. Our results suggest that interventions altering innate or learned food preferences could target habit-directed mechanisms to help mitigate maladaptive eating behavior.

Disclosures: N. Rouhani: None. **C. Grossman:** None. **J.D. Feusner:** None. **A. Tusche:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

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Program #/Poster #: PSTR478.02/O7

Topic: G.03. Motivation

Support: URMC Del Monte SPIN Pilot Grant
SFARI Grant 675250
URMC Department of Psychiatry

Title: Speech perception as inference: indexing top-down effects of prior-knowledge on EEG responses to natural speech

Authors: S. SYNIGAL[1], ***A. NIDIFFER**[2], E. C. LALOR[3], J. THOMPSON[4];
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Abstract: We comprehend spoken language through a sequence of hierarchical stages that transforms complex spectrotemporal acoustic patterns into categorical representations that convey meaning. Based on long-term experience and the ongoing context, our brains form predictions about the acoustic and linguistic content of upcoming speech. At each processing stage, these predictions then interact with the incoming speech signal to shape our perception of that speech. With a view to understanding this inferential process, we sought to characterize neurophysiological indices of speech predictions and their effects on the encoding of speech along the processing hierarchy. We did this by recording electroencephalography (EEG) from participants as they took part in two experiments. In the first experiment, participants listened ~30 minutes of an audiobook. We then modeled how the EEG reflected the acoustic and phonetic features of each word - as a function of how semantically predictable that word was in its narrative context. We found higher modeling accuracy for more surprising words, a result that is consistent with EEG responses indexing prediction error during natural speech comprehension. In the second experiment, participants listened to short, acoustically-degraded sentences that were preceded by a text-based prime that was either matched or mismatched to the content of the sentence. We found a striking behavioral effect of matched (i.e., informative) priors on subjective intelligibility. We again modeled the EEG based on acoustic and linguistic features of the speech stimuli and found higher model accuracy for both acoustic and phonetic features for the mismatched trials. Again, this is consistent with reduced prediction error with informative priors. Finally, we tested for any correlation between the EEG indices of top-down predictions on speech processing obtained from the two experiments - but found none. Finally, we discuss these indices and paradigms and their potential utility in future research on the potentially disrupted role of prediction in perception in certain clinical conditions such as autism spectrum disorder and schizophrenia.

Disclosures: S. Synigal: None. **A. Nidiffer:** None. **E.C. Lalor:** None. **J. Thompson:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

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Program #/Poster #: PSTR478.03/O8

Topic: G.03. Motivation

Support: R01MH131768
R01MH129721
5R21MH122940-02
K23MH115252-01A1

Title: Learning and inference in the development of psychotic symptoms

Authors: J. RODRIGUEZ-SANCHEZ[1], D. MATHALON[2], T. D. CANNON[3], S. W. WOODS[4], ***A. POWERS**[4];
[1]Univ. Col. London, London, United Kingdom; [2]UCSF, San Francisco, CA; [3]UCLA, Los Angeles, CA; [4]Yale Univ., New Haven, CT

Abstract: Hallucinations and delusions are commonly grouped together as the positive symptoms of psychosis, but recent evidence suggests that they may be driven by different and perhaps opposing alterations in learning and inference: a tendency toward delusions (i.e., fixed false beliefs about the world) is accompanied by inappropriate learning, driving new belief formation; by contrast, hallucinations (false inferences about the world's contents) have been shown to relate to the over-weighting of prior knowledge during perception and lack of belief updating.
We will outline specific evidence for delusion- and hallucination-specific alterations in learning and inference, appealing first to fully-formed symptoms and then progressing to their development. We will demonstrate in two large samples of individuals at clinical high risk for psychosis (Ns = 719 and 699) and a separate sample of individuals in their first episode of psychosis (N = 695) that: delusions tend to emerge prior to hallucinations in the vast majority of participants; delusions tend to re-emerge before hallucinations after remission; hallucinations are more stochastic in expression during their development; and delusional severity decreases along with hallucination emergence. We will then examine accompanying electrophysiological evidence in these samples, demonstrating that hallucination emergence corresponds to a reduction in prediction-error signaling and increased top-down information flow on effective connectivity analysis.
Together, these findings support the possibility that the mechanisms driving hallucinations may be a compensatory response to the factors driving delusion formation. We will conclude by examining convergent evidence from genetic abnormalities and environmental exposures known to increase risk for psychosis development, as well as contrasting evidence from non-psychotic hallucinatory syndromes. Finally, we will extend these findings into hypotheses pertaining to learning and inference in psychosis as well as potential interventions that could arrest the emergence of psychotic symptoms in those at high risk.

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Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.04/O9

Topic: G.03. Motivation

Support: NARSAD Young Investigator Award
National Center for PTSD

Title: Altered striatal-dependent stimulus-response learning in posttraumatic stress disorder

Authors: *E. V. GOLDFARB[1], D. T. NGUYEN[1], K. LOETSCHER[1], J. H. KRYSTAL[2];
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Abstract: Posttraumatic stress disorder (PTSD) is a debilitating illness characterized by paradoxical memories for traumatic events: they appear to be both weak (inability to recall key details) and strong (re-exposure elicits distress and reactivity). However, research to date has largely focused on a specific set of regions (hippocampus, amygdala, and medial prefrontal cortex) and tends to emphasize impairments. Based on nonhuman animal and acute stress findings, we tested whether enhancements in a novel memory system - dorsal striatal-dependent memory - play a role in PTSD. We recruited participants with PTSD (N = 25/target 35) and trauma-exposed individuals without PTSD (trauma control, TC: N = 27/35) to complete a set of behavioral tasks designed to assess striatal learning together with fMRI and structural imaging. To assess the formation of these associations, we had participants complete a validated memory guided visual search task (Goldfarb, Chun & Phelps 2016), in which they could form probabilistic stimulus-response (S-R) associations to facilitate performance on a subset of trials. To assess the rigidity of probabilistic S-R associations, we used a novel task in which participants learned to pair stimuli (objects) with responses (rooms) to earn rewards. A subset of these S-R associations were later reversed (requiring flexible response updating), and a separate set of outcomes were later devalued (requiring value updating), both classic tests of "habit" in nonhuman animal models. Results to date provide evidence for stronger and more rigid formation of S-R associations in PTSD, with enhanced striatal structure and function. In the visual search task, participants with PTSD were more accurate at finding the target on S-R trials, a benefit that tracked PTSD symptom severity. Preliminary analyses of neuroimaging data indicate that the putamen marginally contributed to the formation of these S-R associations in PTSD (not TC), especially with more severe symptoms. In the object/room task, participants with PTSD were more rigid, with greater difficulty updating responses after reversal and increased perseveration compared to TC. PTSD symptom severity also tracked impaired devaluation, leading to greater perseveration on previously-rewarded responses. Finally, preliminary structural analyses indicate larger putamen, but not hippocampal, volume tracks more severe PTSD symptoms. These findings provide an important bridge from nonhuman animal models showing that stress and trauma can enhance striatal structure and function, underscoring the need to expand the mechanisms by which memory may contribute to the development and maintenance of PTSD.

Disclosures: E.V. Goldfarb: None. **D.T. Nguyen:** None. **K. Loetscher:** None. **J.H. Krystal:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.05/O10

Topic: G.03. Motivation

Title: Pathways of Social Inference

Authors: D. VIEIRA, N. C. FOLEY, J. K. LEE, *G. H. PATEL;
Columbia University/NYSPI, New York, NY

Abstract: Introduction: Making inferences about people's thoughts and feelings requires the real-time integration of complex dynamic sensory information with ongoing theory-of-mind (ToM) operations. The temporoparietal junction (TPJ) and superior temporal sulcus (STS) contain areas relevant to face-emotion recognition, processing of speech, visual attention, and ToM. Here we detail how these areas form the basis of three TPJ-STS social inference pathways, relate them to distinct functions, and show how they are disrupted in schizophrenia (Sz), which is associated with poor social functioning.
Methods: We collected BOLD-fMRI data from participants watching a 12-minute audio/visual movie clip (22 healthy controls (HC), 24 Sz participants (SzP)), watching a 15-minute visual-only movie clip (27 SzP, 21 HC), listening to a 7.5-minute audio-only story (23 HC, 20 SzP), or at rest (target of 22 minutes, all participants). We clustered (k-means) the audio/visual and visual-only BOLD time-courses into co-activation pattern (CAP) states and then examined the association of these CAP states with movie features and saccades. We also used weighted shortest path length (wSPL) from each region of interest (ROI) to either right A1 or V1 to quantify the stimulation-induced changes in synchronization from rest.
Results: We found three CAP states that involved the TPJ-STS and were associated with social cues ($pFDR<0.05$). The first CAP state encompassed visual processing/attention areas, TPJ, pSTS, and STS; corresponded to visual motion and saccades; and was less associated with socialness for SzP in the visual-only movie. The second CAP state encompassed late visual areas, TPJ, pSTS, STS, and STG; corresponded to presentations of socialness, faces, and speech—especially ambiguous expressions of emotion in speech—and in SzP was less associated with all of these features plus motion. The third CAP state encompassed auditory, STG, STS, and TPJ; corresponded primarily with speech, socialness, and sarcasm; and in SzP differed in association for all of these but not motion. wSPL analyses demonstrate that TPJ-STS areas synchronize more with both V1 and A1 in movie-watching than rest and is increased in SzP versus HC ($p<0.05$).
Conclusion: These results support the existence of three overlapping but distinct pathways for social inference in the TPJ-STS—one associated with the visual scanning for facial expressions, another with the integration of facial expressions and speech, and another for speech processing. SzP demonstrate abnormalities in all three pathways, suggesting that failures to properly use sensory information to make social inferences impact social functioning.

Disclosures: D. Vieira: None. **N.C. Foley:** None. **J.K. Lee:** None. **G.H. Patel:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.06/

Topic: G.03. Motivation

Support: DA050410
DA042111
DA048931

Title: A cocaine-activated ensemble exerts increased control over behavior while decreasing in size

Authors: K. THIBEAULT[1], M. Z. LEONARD[2], V. KONDEV[3], S. D. EMERSON[4], R. BETHI[1], J. P. SENS[5], A. J. LOPEZ[1], B. P. NABIT[1], H. ELAM[2], D. G. WINDER[6], S. PATEL[7], D. D. KIRALY[8], B. A. GRUETER[9], ***E. CALIPARI**[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Pharmacol., Vanderbilt Univ., Nashville, TN; [3]Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Vanderbilt Univ., Durham, NC; [5]Neurosci., Mayo Clin. Grad. Sch., Jacksonville, FL; [6]Univ. of Massachusetts Chan Med. Sch. Grad. Program in Neurosci., Worcester, MA; [7]Psychiatry and Mol. Physiol., Vanderbilt Univ. Med. Ctr., Nashville, TN; [8]Physiol. / Pharmacol., Wake Forest Sch. of Med., WINSTON SALEM, NC; [9]Anesthesiol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Repeated exposure to drugs of abuse causes adaptations in both neural function and behavior. A large amount of work has focused on defining the mechanisms by which these changes occur. While numerous studies have investigated the molecular, cellular, and circuitry changes induced by drugs of abuse in the nucleus accumbens (NAc), many studies have focused on gross, genetically-identified populations. However, only a subset of cells in any brain region are activated by any stimulus - termed ensembles. There remains a fundamental gap in understanding whether ensembles within the NAc are recruited by drugs of abuse and act as the primary drivers of the maladaptive behavioral responses in substance use disorder (SUD). Here we show that small functional populations of cocaine-activated neurons acquire a new ability to control drug reinforcement behavior over time. Using the Arc-CreER^{T2} mouse line, in conjunction with optogenetic tools and behavioral paradigms, we show that the neuronal ensembles tagged by *Arc* represent a unique population as compared to ensembles purely labeled by *c-Fos*. We first show that while *c-Fos*-labeled-ensembles increase over repeated cocaine exposure, the *Arc*-labeled ensemble is reduced in size. Using microendoscopic imaging with calcium sensors, we show that cocaine suppresses more cells than it activates, and - consistent with the *Arc* ensemble labeling - the small, activated population is reduced over repeated exposure. Further, repeated cocaine alters the physiology of *Arc*+ neurons and changes their ability to support and modulate behavior. Lesioning the ensemble recruited by repeated - but not acute - cocaine attenuated cocaine-related behaviors, such as cocaine self-administration. Overall, these results suggest that different IEGs label different neuronal ensembles, and *Arc*+ ensembles play important roles in cocaine-induced behavior. Importantly, repeated cocaine

administration alters *Arc*+ neuronal ensembles, modulating their behavioral output, and establishing these neuronal ensembles as necessary for cocaine self-administration.

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Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.07/O11

Topic: G.03. Motivation

Title: Attentional priority and limbic activity favor gains over losses

Authors: *K. HU[1], E. DE ROSA[2], A. K. ANDERSON[2];
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Abstract: Prospect theory suggests decisions reflect a bias toward avoiding losses compared to equivalent gains. However, whether this bias extends to lower-level perceptual processes remains unclear. We examined if losses are prioritized over gains in temporal order judgment performance. In Study 1 (n=148), participants judged the temporal order of rapidly presented gain and loss-associated stimuli. Despite equal reinforcement, participants exhibited a striking bias perceiving gain stimuli as appearing first relative to loss stimuli. Individual differences in regulatory focus moderated this effect, with prevention-focused individuals showing greater loss aversion. In Study 2 (n=34), fMRI measured neural responses during the task. Gains and losses similarly engaged the mesocorticolimbic reward system, including the ventral tegmental area (VTA), nucleus accumbens, and anterior insula. However, individuals with greater VTA response to gains versus losses showed a corresponding bias perceiving gains as appearing first. Mediation analysis revealed this bias was influenced by both VTA reactivity and regulatory focus orientation. Contrary to attention-based accounts, losses did not attract more attention than gains. Nor did losses produce greater emotional responses, counter to contrast-based theories. Instead, individual differences in motivational orientation and reward reactivity contributed to the well-established phenomenon of loss aversion in higher-order decision-making. These findings elucidate the perceptual and neural underpinnings of loss aversion and highlight its origins in differences in salience processing.

Disclosures: K. Hu: None. **E. De Rosa:** None. **A.K. Anderson:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

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Program #/Poster #: PSTR478.08/O12

Topic: G.03. Motivation

Support: R01MH125564
BSF grant no. 2019801

Title: Correspondence between computational decision-making phenotypes and transdiagnostic clinical symptomatology across development

Authors: *N. GOLDWAY[1], Q. YANG[1], S. Y. NIELSEN[1], L. SOLOMYAK[2], S. ZOROWITZ[3], E. ELDAR[2], Y. NIV[3], C. A. HARTLEY[1];
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Abstract: Psychiatric disorders like depression, anxiety, OCD, and ADHD often arise in childhood and adolescence. Although maladaptive learning and decision-making processes are implicated in these disorders, the underlying computational mechanisms remain unclear. Our study aims to characterize developmental changes in computational decision-making phenotypes and their relation to transdiagnostic psychiatric symptoms across development. To date, 710 participants (target n=1000) aged 10-25 have completed the study and were split into discovery (n=425) and replication samples (n=285). Participants completed three reinforcement-learning tasks assessing model-free versus model-based control, Pavlovian versus instrumental learning, and positive versus negative outcome weighting, as well as self-report questionnaires assessing transdiagnostic psychiatric symptomatology. A subset of 170 participants completed a re-test session after two weeks. Tasks showed robust test-retest reliability for computational model parameters (risk-sensitivity: mean r=.77, go-no-go learning: mean r=.78, two-step task: mean r=.72). Factor analysis revealed four latent symptom dimensions; general symptom severity, anxious rumination, emotional dysregulation and anhedonia. Mixed-effects regression models with task parameters and age as predictors showed that anxious rumination was greater in older participants ($p < .001$), and those who exhibited increased model-based planning ($p < .01$) and decreased learning from positive prediction errors ($p < .05$). Emotional dysregulation was decreased with age ($p < .001$), and was greater in those with reduced model-based planning ($p < .05$), decreased learning from negative outcomes ($p < .05$), and their interaction ($p < .05$). These results demonstrate that latent cognitive computations that underpin clinically relevant behaviors contribute to the emergence of transdiagnostic psychiatric symptoms across development.

Disclosures: N. Goldway: None. **Q. Yang:** None. **S.Y. Nielsen:** None. **L. Solomyak:** None. **S. Zorowitz:** None. **E. Eldar:** None. **Y. Niv:** None. **C.A. Hartley:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.09/O13

Topic: H.03. Decision Making

Support: ONR Grant N00014

Title: E-i pathway balance introduced by three-factor learning can explain visuomotor mismatch and deviation detection in a parsimonious model

Authors: *J. MENG, X.-J. WANG;
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Abstract: The brain, far from being a passive sensory information receiver, actively generates predictions about the external world. These predictions, crucial for survival, allow us to focus more on surprise signals than known events. To calculate these “surprises,” neural circuits often need to compare an innate prediction and incoming sensory information initiated in different brain regions through subtraction. However, the long-range synapses between brain areas are dominantly excitatory, suggesting interneurons (IN) are involved in flipping long-range excitation into local inhibition. One experimental protocol is to study how visual response varies depending on whether it can be predicted through self-generated motions, where the prediction is closely related to the motion signal. Another protocol is to study the response to an oddball stimulus after a series of normal ball stimuli, where the prediction is generated through historical information. Here, we develop a parsimonious model with multiple IN subtypes to reproduce experimental observations from these two predictive coding protocols. We first show that a three-factor learning rule on the inhibitory synapses can introduce pathway E-I balance during the visuomotor coupling. After learning, positive and predictive error neurons both emerge in the circuit. Importantly, the global response in the model is positive because the activity is bound above zero. Next, to study the oddball protocol, we use an integrator, which gradually accumulates information through the incoming stimuli, to provide prediction, contrasting the motion signal in the previous case. Through competition between different integrators, the circuit responds more strongly to the stimuli presented as an oddball than presented as a random control. Furthermore, our model highlights that the deviant detection neurons observed in the oddball protocol should be the same positive prediction error neurons as those observed in the visuomotor coupling protocol. We predict the detailed response of interneurons in these two protocols, which can be tested in the experiments. Our model offers a unified biologically feasible platform to study predictive coding.

Disclosures: J. Meng: None. **X. Wang:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.10/O14

Topic: G.03. Motivation

Support: NIH K99NS128075

Title: Aberrant updating of priors in mouse models of Autism

Authors: *J.-P. G. NOEL;
Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Computational psychiatry has suggested that humans within the autism spectrum disorder (ASD) inflexibly update their expectations (i.e., Bayesian priors). Here, we leveraged high-yield rodent psychophysics (n = 75 mice), extensive behavioral modeling (including principled and heuristics), and (near) brain-wide single cell extracellular recordings (over 53k units in 150 brain areas) to ask (1) whether mice with different genetic perturbations associated with ASD show this same computational anomaly, and if so, (2) what neurophysiological features are shared across genotypes in subserving this deficit. We demonstrate that mice harboring mutations in *Fmr1, Cntnap2,* and *Shank3B* show a blunted update of priors during decision-making. Neurally, the differentiating factor between animals flexibly and inflexibly updating their priors was a shift in the weighting of prior encoding from sensory to frontal cortices. Further, in mouse models of ASD frontal areas showed a preponderance of units coding for deviations from the animals' long-run prior, and sensory responses did not differentiate between expected and unexpected observations. These findings demonstrate that distinct genetic instantiations of ASD may yield common neurophysiological and behavioral phenotypes.

Disclosures: J.G. Noel: None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.11/

Topic: G.03. Motivation

Support: NIH Grant F31AA031439
NIH Grant R21AA027629

Title: Effects of Chronic Low-dose Ethanol on Reward Motivation and Valuation

Authors: *C. M. CURRAN-ALFARO[1], K. G. BRYANT[2], W. COREY[3], C. SHEEHAN[4], S. AMIN[5], C. SIDE[3], J. M. BARKER[3];
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Abstract: A majority of adults in the US consume alcohol at casual drinking levels. Recent work increasingly identifies the potential for lower-dose alcohol to impact both brain and behavior - including risk for alcohol use disorder (AUD). We previously found that chronic exposure to low-dose ethanol increases reward motivation in male, but not female, mice, which may reflect underlying alterations in behavioral response to changes in reward value. To assess sensitivity to change in value we measured differences in motivated behavior in a progressive ratio (PR) task. Adult male and female C57BL6J mice were trained to operantly self-administer sucrose. Mice received either a low-dose ethanol (0.5g/kg) or saline injection 1-hour after each session. Sensitivity to change in reward value was assessed in counterbalanced PR tests in which sucrose reward magnitude was changed. When reward magnitude was decreased, two populations of ethanol-exposed females emerged: one increased responding, while another reduced responding (chi-square; $p < 0.05$), suggesting that low-dose ethanol exposure selectively changed sensitivity to reduced reward magnitude in females. Both groups of male mice maintained responding. To assess sensitivity outcome devaluation, mice consumed sucrose in a 2 bottle-choice drinking paradigm. Mice received either low-dose ethanol (0.5g/kg) or saline injection 1-hour after sucrose access. Sucrose was devalued using lithium chloride (LiCl)-induced conditioned taste aversion in which 0.15M LiCl or vehicle was administered immediately after sucrose consumption for 3 days. Both control and ethanol LiCl males reduced sucrose consumption after devaluation. While control females also reduced sucrose consumption after devaluation, ethanol-exposed females were insensitive to LiCl devaluation. These findings revealed sex-specific effects of chronic low-dose ethanol on sensitivity to changes in reward value. To begin to identify neurobiological targets impacted by chronic low-dose ethanol exposure, we quantified expression of cFos - an immediate early gene - following induced by reward seeking. We found increased cFos in medial prefrontal cortex subregions in ethanol-exposed female mice vs controls, while ethanol-exposed males exhibited greater subcortical cFos than controls. Ongoing work is investigating the effects of chronic low-dose ethanol on value-guided behavior in a novel task. Our findings point to persistent neurobehavioral alterations resulting from chronic exposure to low doses of alcohol, and have the potential to inform our understanding of alcohol-associated comorbidities and the transition to AUD.

Disclosures: C.M. Curran-Alfaro: None. **K.G. Bryant:** None. **W. Corey:** None. **C. Sheehan:** None. **S. Amin:** None. **C. Side:** None. **J.M. Barker:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.12/O15

Topic: H.03. Decision Making

Support: the STI2030-Major Projects (2021ZD0204200)
the Sino-German Center for Research Promotion (M-0705)
the National Natural Science Foundation of China (31871136)

Title: How humans solve complex visual problems: a feature-based visual attention generative model

Authors: *L. YE[1,2], L. HUANG[3,4], K. ZHOU[5], M. MENG[1,2];
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Abstract: People often rely on intuition to provide quick but imperfect solutions for complex problems. Here, intuition-based problem-solving is studied in a classic combinatorial optimization problem: the Traveling Salesman Problem (TSP). In the TSP, a salesman aims to find the shortest path traversing specified cities (nodes) and returning to the starting point. The TSP is a well-known NP-hard problem, but humans often can produce quick heuristic solutions just by eyeballing, presumably through some approximation algorithms. How does the brain construct generative models from sensory data to solve such problems? Here, we combined computational modeling with a large-scale behavioral study, which simulates the Euclidean TSP through an online game on a smartphone app platform, collecting over 360 million valid behavioral responses on 150,000 stimulus patterns. We first trained a deep neural network to predict human performance, using it as a benchmark. Next, we proposed a new heuristic - the minimum enclosing circle heuristic - as a baseline model. Finally, we developed a feature-based visual attention generative model, incorporating stimulus distance, angle, configuration, spatial distribution, and minimum spanning tree. This 25-parameter model not only achieved high accuracy in fitting human performance, but also, unlike deep learning models, remained parsimonious and interpretable. Our model suggests that the visual system can modulate the allocation of visual attention, extracting accurate salient information through multi-level features to simplify problem representation and rapidly approach approximate optimal solutions. This work provides a novel framework for examining cognitive mechanisms of how humans solve complex problems such as the TSP based on visual intuition, contributing to understanding and simulation of human intelligence and heuristic decision-making processes.

Disclosures: L. ye: None. **L. Huang:** None. **K. Zhou:** None. **M. Meng:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.13/O16

Topic: H.13. Schizophrenia

Title: Systematic Review of Neuroimaging Findings in Schizophrenia: Unveiling the Brain's Complexity

Authors: *N. CAVUS;
Neurosci., Yeditepe Univ., ISTANBUL, Turkey

Abstract: Schizophrenia is a severe and debilitating psychiatric disorder characterized by disturbances in thought, perception, emotion, and behavior. Neuroimaging techniques have significantly advanced our understanding of the neurobiological basis of schizophrenia. This systematic review aims to comprehensively analyze and synthesize the current body of literature on neuroimaging findings in schizophrenia.
The review begins by providing an overview of schizophrenia, including its epidemiology, clinical presentation, and current diagnostic criteria. It then explores the role of neuroimaging in schizophrenia research, highlighting the various techniques used, including structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).
Structural neuroimaging studies have consistently reported abnormalities in brain structure in individuals with schizophrenia. These include volumetric reductions in gray matter, particularly in the frontal and temporal lobes, as well as enlargement of the lateral and third ventricles.
Functional neuroimaging studies have revealed alterations in brain function and connectivity, with aberrant activity observed in several brain regions, including the prefrontal cortex, hippocampus, and thalamus. Diffusion imaging studies have shown disruptions in white matter integrity, suggesting alterations in brain connectivity in schizophrenia.
The review then discusses the potential clinical implications of neuroimaging findings in schizophrenia, including the identification of biomarkers for early diagnosis, prediction of treatment response, and monitoring of disease progression. Neuroimaging may also help elucidate the underlying pathophysiological mechanisms of schizophrenia, leading to the development of novel therapeutic interventions.
Finally, the review concludes with a discussion of future directions for neuroimaging research in schizophrenia, including the need for larger, multicenter studies, longitudinal imaging studies, and the integration of neuroimaging data with other biological markers, such as genetic and neurocognitive measures.
Overall, this systematic review provides a comprehensive overview of neuroimaging findings in schizophrenia, highlighting the significant contributions of neuroimaging techniques to our understanding of the neurobiology of this complex disorder.

Disclosures: N. Cavus: None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

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Program #/Poster #: PSTR478.14/O17

Topic: G.03. Motivation

Support: P50 MH096889
R21AG072673

Title: Early-life unpredictability modulates planning horizon in a structured foraging task

Authors: *Y. CHEN[1], N. C. HARHEN[1], D. M. STOUT[2,3], A. M. BORNSTEIN[1,4];
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Abstract: Early-life and adult adversities are known to have multiple long-lasting impacts on decision-making under uncertainty, and they are often associated with deleterious psychopathological outcomes, such as anhedonia, depression, and anxiety. However, the specific aspects of the decision-making process affected by these adversities and whether their long-term health outcomes are mechanistically distinct remain unclear. A possible common mechanistic impact of adverse experiences is their influence on an individual's response to uncertainty. Normative analysis has demonstrated that when navigating uncertain state-spaces, individuals should respond to uncertainty by reducing their planning horizon, a prediction that we have previously confirmed holds in a broad population. Here, we examine whether early-life experiences of unpredictability (ELU) and/or adult trauma exposure amplify this rational sensitivity to uncertainty within a structured decision-making task. 297 participants were tasked with completing a patch-leaving ("foraging") task with a complex state-space that required inferring latent structure, along with the Questionnaire of Unpredictability in Childhood (QUIC), the Life Event Checklist (LEC-5), and the Post-Traumatic Stress Disorder Checklist (PCL-5). Our results reveal that ELU is associated with a greater decline in planning horizon, specifically in response to task uncertainty, and that this effect does not extend to lifelong trauma exposure, consistent with a theoretical model specifying a critical period of sensitivity to associative unpredictability. Moreover, unpredictability in the parental and physical environment appear to be the key factors influencing individuals' planning behaviors. The results highlight how ELU impacts specific decision-making components and potentially contributes to our understanding of the long-term consequences of ELU on decision-making and mental health.

Disclosures: Y. Chen: None. **N.C. Harhen:** None. **D.M. Stout:** None. **A.M. Bornstein:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

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Program #/Poster #: PSTR478.15/O18

Topic: G.03. Motivation

Support: 7R01DA054201
1TL1TR003019

Title: The neural mechanisms underlying how food craving biases subjective valuation and choice

Authors: *E. M. SCHWEITZER[1], S. GRUNEVSKI[2], Z. BARAKCHIAN[3], J. KONG[4], A. B. KONOVA[3];
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Abstract: Food craving is a ubiquitous experience that profoundly influences dietary choice and thus physical and mental health. Yet the psychological and neural mechanisms of food craving, and especially its behavioral intent component, remain poorly understood. Past work has implicated brain regions associated with reward valuation and emotion/interoceptive processes in craving. However, this work has mostly focused on passive cue-reactivity paradigms unable to probe how craving intersects with valuation and choice. We previously found craving transiently transforms behavioral indices of subjective value for craved and similar options, but not dissimilar ones (e.g., craving a chocolate bar scales subjective value for other chocolaty snacks, but not equally tasty cheesy ones), demonstrating how craving may narrow and focus motivation for the object of craving. To understand how such scaling and similarity effects emerge, we examined changes in fMRI activity within a putative craving circuit in an incentivized decision-making task, before and during craving. We also explored how problematic food-related behavior (assessed via screening measures) may moderate these effects. Participants (N=32) repeatedly reported their momentary willingness to pay (WTP, indexing current subjective value) for palatable snack foods before and after a multisensory craving induction designed to elicit craving for one of the snacks. Behaviorally, participants showed significant and selective increases in WTP for the craved snack, with this effect more pronounced when snacks were offered in higher quantities. Participants with higher food-related symptomatology additionally displayed significant decreases in WTP for dissimilar snacks, showing an even greater disparity in subjective valuation between craved and non-craved snacks during craving. Neurally, we found canonical value regions (ventromedial prefrontal cortex and ventral striatum) tracked changes in WTP, while the amygdala and insula specifically tracked attribute-similarity across choice options. These patterns were enhanced post-craving induction, but only value encoding in ventral striatum related to food-related symptomatology. These findings suggest canonical value regions and emotional/interoceptive regions may work together within the broader putative craving circuit to bias decision-making during craving, and that downstream processes related to value computation may facilitate problematic food-related behaviors.

Disclosures: E.M. Schweitzer: None. **S. Grunevski:** None. **Z. Barakchian:** None. **J. Kong:** None. **A.B. Konova:** None.

Poster

PSTR478: Higher Cognition: Priors and Inference

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR478.16/O19

Topic: G.03. Motivation

Title: Towards a memory flow theory: redefining the flow state through neuroscience meta-analysis

Authors: *M. SHEHATA[1,2,3];
[1]Caltech, Pasadena, CA; [2]Institute for Research on Next-Generation Semiconductor and Sensing Science, Toyohashi University of Technology, Toyohashi, Japan; [3]Filicit, Inc., La Crescenta, CA

Abstract: [Introduction]: The flow state, characterized by optimal performance and focus, has garnered significant attention. However, recent reviews (Peifer et al., 2022; Alameda et al., 2022) highlight limited and inconclusive neuroscience evidence, hindering theoretical development. This meta-analysis expands the scope beyond studies explicitly focused on "flow." We analyze tasks across neuroscience fields including expertise, learning, memory, reward, and positive emotions to potentially induce flow states, aiming to refine flow dimensions. [Methods and Results]: We analyzed tasks potentially conducive to flow states, regardless of the original study's primary aim. So far, our analysis included 35 tasks from 50 studies. Since the flow state is characterized by a balance of high skills and challenge, and skills are intrinsically linked to learning and memory, we used memory encoding and recall mechanisms as a framework to redefine the flow state. Next, to refine the temporal characteristics of the flow state, we leverage the psychophysics of the reward system. Specifically, we focus on the timing of stimulus-response (St-Rs) and stimulus-stimulus (St-St) intervals. Research suggests that the brain thrives on efficient prediction. When rewards are delivered consistently within a specific time window, the reward system becomes primed for anticipation. Hence, the St-Rs/St-St window may be a critical factor influencing the emergence of the flow state. Our analysis of the included tasks suggests that this window might reside between 100 milliseconds and 5 seconds, although further empirical investigation is necessary. [Conclusion]: Our framework integrates insights from attention, working memory, learning, memory, reward, emotion, volition, proprioception, and time perception. It explores the use of psychophysical parameters to objectively define the flow state. This work offers principles for designing flow-focused neuroscience experiments in humans and animals. Moreover, we discuss that the flow state's evolutionary significance may extend beyond performance enhancement, potentially linked to the evolution of learning, memory, and reward systems. [Limitations]: Meta-analytical constraints inherently introduce gaps. Dedicated empirical studies are needed to validate each redefined dimension rigorously.

Disclosures: M. Shehata: None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.01/Web Only

Topic: G.03. Motivation

Support: NSFC U1805263
HSSF-MEC 23YJAZH183

Title: Cross-species affective interaction modeling

Authors: *C.-Y. LIU, B. YIN;
Sch. of Psychology, Fujian Normal Univ., Fuzhou, China

Abstract: This research pioneers the development of foundational models for understanding and enhancing affective interactions across species, drawing on principles from affective neuroscience and comparative psychology. We introduce three models: the Affective Threshold Model, the Dynamic Set-Point Model, and the Affective Schema Model, each derived from in-depth analyses of interspecies communications. These models elucidate how various species process affective information and respond to environmental stimuli, emphasizing the evolutionary continuity of affective pathways. The Affective Threshold Model explores the initial perception and reaction thresholds to affective stimuli. The Dynamic Set-Point Model elaborates on the adaptive mechanisms that regulate affective states in response to changing environments. Lastly, the Affective Schema Model delves into the learned affective responses and their neural underpinnings across different contexts and experiences. Together, these models provide a robust theoretical framework for understanding the complex dynamics of affective interactions among diverse species, offering insights into the fundamental processes that govern affective communication in the natural world.

Disclosures: C. Liu: None. **B. Yin:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.02/O20

Topic: G.03. Motivation

Support: NIDA DA047976
NIMH MH129310

Title: Social isolation increases the motivation for social interaction

Authors: *A. PACHECO-SPIEWAK[1], M. VENNIRO[2];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Background: Social isolation is a stressful life experience that can induce and exacerbate the severity of neuropsychiatric disorders. The current epidemic of loneliness and isolation necessitates a thorough exploration of the behavioral and mechanistic aspects of social isolation. Here, we used a model of voluntary social interaction to examine the impact of social isolation during adolescence on operant social interaction.**Methods:** Male and female rats were weaned from their mother at post-natal day (PND) 21 and separated into either isolated or grouped housing conditions for a total of 3 weeks. At PND 42, we trained isolated and grouped

rats to self-administer social interaction at increasing fixed-ratio (FR) schedules (2 h/day - FR1 (5 sessions), FR2 (2 sessions), FR4 (2 sessions), FR8 (2 sessions) and we used age-matched and sex-matched social partners. **Results:** We found that, independent of sex or FR requirements, rats who were socially isolated during adolescence were more motivated to seek social interactions, earning more social rewards compared to their group-housed counterparts. **Conclusion:** Our results demonstrate that social isolation strengthens the incentive for social interaction. These findings highlight the importance of social isolation-induced stress and its effect on social behavior.

Disclosures: A. Pacheco-Spiewak: None. **M. Venniro:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Topic: H.06. Social Cognition

Support: NIH Grant R01AG071787

Title: The effect of early life stress on prosocial behavior in mice

Authors: *H. LEE, J. LU, Y. ZUO;
Molecular, Cell and Developmental Biol., Univ. of California Santa Cruz, Santa Cruz, CA

Abstract: The environment we live in shapes how we perceive and interact with the world. Interactions with conspecifics are an essential part of the life of social animals. Many species, ranging from insects to humans, exhibit a rich repertoire of prosocial behaviors, including sharing, cooperation, and other forms of caring and helping. According to the perception-action model (PAM), prosocial behavior begins with the perception of emotional signals from others conditioned by the observer's experiences and results in appropriate helping behaviors. Recent studies show that mice exhibit prosocial behaviors such as allogrooming toward distressed conspecifics (consolation-like behavior). Here, we demonstrate that early-life experiences alter the mouse's behavioral response to the emotions of others. We found that socially isolated mice show reduced prosocial behavior toward distressed mice with abnormal social interactions. To separate the perceptual phase of prosocial behavior from the action phase, we designed a test for emotional discrimination in mice. The observer mouse was exposed to two demonstrators confined in wire containers, one of which had been previously subjected to restraint stress and the other one had not. We measured the time spent by the observer on each demonstrator and calculated a discrimination index. Mice subjected to social isolation from weaning showed impaired emotion discrimination. Interestingly, 2 weeks of social isolation from weaning was sufficient to induce the behavioral deficits, but the same duration of social isolation during adulthood had no effect. Additionally, the defective emotional discrimination induced by social isolation from weaning could not be rescued through resocialization. These results suggest that

early life stress influences prosocial behaviors via impaired emotional perception and has long-lasting effects. We are examining brain activity patterns for PAM of prosocial behavior, which will allow us to dissect neuronal mechanisms of perception and action for higher cognitive functions.

Disclosures: H. Lee: None. **J. Lu:** None. **Y. Zuo:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Program #/Poster #: PSTR479.04/O22

Topic: G.03. Motivation

Support: NIDA DA047976
NIMH MH129310

Title: Modeling volitional social reciprocity

Authors: *C. A. LIS[1], R. MADANGOPAL[2], K. PAPASTRAT[3], Z. HUANG[3], A. PACHECO-SPIEWAK[3], M. VENNIRO[4];
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Abstract: Background: Reciprocal social interactions are essential for cohesive societies and fostering cooperation among organisms. While animal models are commonly used to study social behaviors, they lack the motivational component of reciprocity. Here, we developed a model where resident and partner rats volitionally coordinate actions, requiring increased effort to reciprocate social interactions and investigated its underlying mechanisms. **Methods:** In our model, the resident rat initiates the interaction by pressing a lever to activate cues for the partner, who then reciprocates by pressing an additional lever, leading to social interaction. Next, we increased the effort for both residents and partners to reciprocate, both concurrently and separately. Next, we manipulated the norepinephrine system both systemically and centrally during volitional reciprocal social interactions. **Results:** Both male and female paired rats consistently demonstrate reciprocal motivation to engage in social interaction, regardless of their roles. Rats effectively coordinate their actions, maintaining low latency to achieve interaction and a high frequency of interactions even when the effort request is increased. When we analyzed behavioral performances and created a cumulative social score, we found a significant proportion of paired rats showing heightened motivation to engage in voluntary reciprocal social interactions. Furthermore, by manipulating the norepinephrine system either systemically using pharmacological interventions or by central lesioning, we selectively disrupted the distribution of paired rats highly motivated for voluntary reciprocal interaction. Importantly, this manipulation

did not affect motivation related to food rewards. **Conclusions:** We offer insights into fundamental behavioral and neurobiological mechanisms underlying reciprocal social interactions and complex social structures.

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Poster

PSTR479: Motivation: Social Communication and Behavior II

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Program #/Poster #: PSTR479.05/O23

Topic: G.03. Motivation

Support: NIH DA047976
NIMH MH129310

Title: A cerebellar-thalamic projection mediating social desire

Authors: *Z. HUANG[1], A. PACHECO-SPIEWAK[2], C. LIS[3], K. PAPASTRAT[2], L. A. RAMSEY[5], M. VENNIRO[4];
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Abstract: Background: Social interactions are highly rewarding, and periods of social isolation amplify the desire for social engagement in humans. Here, we developed a rodent model to mimic social craving and identify the neural circuitry responsible for heightening social desire during periods of social isolation. **Methods**: We trained male and female rats first for food (2h/d, 6d) and then for social (2h/d, 12d) self-administration. Next, we assessed social desire after 1 and 14 days of social deprivation. During late social deprivation test, we identified the brain-wide social desire-related activated brain regions (using the activity marker Fos). Next, using chemogenetic tools, we investigated the roles of the cerebellum and its projection to the ventromedial thalamus in motivation to seek social interaction. **Results**: Independently of sex, social desire in the seeking test was higher after 15 days of social deprivation than after 1 day, demonstrating the intensification of social craving as reported in humans. Social desire was associated with selective activation of several brain regions spanning from cortical areas, amygdala regions, and cerebellum. After 15 days of social deprivation, chemogenetic inhibition of the cerebellum, and a selective inhibition of the deep cerebellar nuclei-to-ventromedial thalamus projection decreased social desire in both male and female rats. **Conclusion**: We introduced a novel social desire rat model and identified novel roles of the cerebellum and its projection to ventromedial thalamus in the expression of increased motivation to seek social interaction during periods of social deprivation.

Disclosures: Z. Huang: None. **A. Pacheco-Spiewak:** None. **C. Lis:** None. **K. Papastrat:** None. **L.A. Ramsey:** None. **M. Venniro:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.06/O24

Topic: G.03. Motivation

Support: JSPS KAKENHI 22H04855
Neuroglobal Program

Title: Uncovering social motivations in daily dialogue modes: an fMRI study

Authors: *Y. HAN[1], Y. HUANG[1], S. SHIRAHAMA[1], A. TAKEMOTO[2], H. JEONG[1], M. SUGIURA[2];
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Abstract: In our daily communication, various motivations drive the continuation of social conversations. However, the social motivations from multidimensional and neural perspectives are unexplored. In this study, to categorize motivations driving continuous conversation ("Dialogue modes") and understand the psychological mechanisms in each motivation, two experiments were conducted. First, we conducted two behavioral social surveys regarding recent enjoyable chats including an open-ended qualitative study (n=300) and a quantitative survey with 59 candidate questionnaire items (n=1200) to determine the major dialogue modes. The four main modes were categorized by factor analysis: Relief (relieving worries and tension), Novelty (exposure to new things such as people and information), Comfort (casual chatting with familiars/relaxed vibes), and Interest (leisure conversations).
Secondly, to examine neural underpinnings in the four dialogue modes, 37 participants performed reciprocal conversation tasks that involved participants interacting with short conversational videos (duration 5 ± 2 seconds) of human-like avatars inside fMRI. The conversation tasks consisted of 2 phases- S1 (initiating a chat by the provided sentences) and S2 (listening to the avatar's replies and responding freely). Outside the scanner, participants rewatched the videos and evaluated the motivation level for each stimulus. The behavioral ratings and neural responses (S2 phase) were computed to analyze the neural correlates of the mode-relevant (MR) or mode-specific motivation (MM) by manipulating the motivational scores. It is mode-relevant (MR) without motivation scores, and motivation scores are included in mode-specific motivation (MM). The results showed precuneus activation in Relief (MR), deactivation in the bilateral inferior parietal cortex (MR) and parieto-occipital sulcus (MM) in Novelty, left inferior parietal cortex activation (MR), and left insula deactivation (MM) in Comfort, and deactivation of right anterior middle temporal gyrus and bilateral temporoparietal junction in Interest (MR). The study suggests that satisfying emotional needs through enjoyable conversation fosters social motivation for continued interaction. People in a nervous situation may seek reassurance through finding self-other association in Relief mode and friendly small chitchats may lessen pessimistic thoughts in Comfort mode. In conclusion, enjoyable

conversations tend to ease negative feelings and promote continued dialogue by sharing common worries and through casual talks.

Disclosures: Y. Han: None. **Y. Huang:** None. **S. Shirahama:** None. **A. Takemoto:** None. **H. Jeong:** None. **M. Sugiura:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.07/O25

Topic: G.03. Motivation

Support: NIGMS MOSAIC K99/R00 Award
Helen Hay Whitney Foundation
NIH232MH015144

Title: Oxytocin-mediated circuit connectivity and its role in social motivation

Authors: *B. UCEDA-ALVAREZ[1], E. RODRIGUEZ[1], C. ADEYEMI[1], H. IBARRA AVILA[4], C. LEE-KONG[1], M. THURNHERR[1], C. D. SALZMAN[1,2,3];
[1]Zuckerman Inst., [2]Dept. of Neurosci., [3]Dept. of Psychiatry, Columbia Univ., New York, NY; [4]Cell. Imaging Platform, Zuckerman Inst., New York, NY

Abstract: Social behavior often is based on the ability to assign social value to stimuli, and then to direct emotionally appropriate motivated behavior. We currently lack a mechanistic understanding for how representations of stimuli can lead to these socially-driven behavioral and emotional responses. One type of important social information is the hierarchical rank of individuals within a social group. Data from our lab has shown that activity in a pathway from the anterior cingulate cortex to the basolateral amygdala (ACC-BLA) is necessary for socially-motivated investigative behaviors elicited by the presentation of urine odors from socially-ranked mice. Previous research has found that oxytocin enhances the signal-to-noise ratio of sensory stimuli, thereby enhancing neural signal transmission and strengthening neural synchrony, which could serve to enhance the saliency of social stimuli. We hypothesize that urine odors taken from socially-ranked mice may differentially activate oxytocin receptor positive (OXTR+) neurons in the ACC, leading to the observed differences in investigative behaviors. To validate this hypothesis, we are determining the connectivity of OXTR+ neurons in the ACC and the necessity of OXTR+ ACC-BLA neurons for socially-motivated behavior through a combination of optogenetic manipulations, behavioral assays, viral tracing, and electrophysiological recordings. Our data shows that a subset of OXTR+ neurons in the ACC is activated by socially-ranked conspecific odors, providing evidence that this region plays a role in the encoding of social information. These neurons were also found to form reciprocal connections with neurons in the BLA. Optogenetic-assisted whole-cell patch-clamp recordings confirmed direct excitatory input from OXTR+ ACC neurons onto BLA neurons. However, our

molecular characterization of OXTR+ ACC neurons indicates that there is a mixture of excitatory and inhibitory neurons. Future experiments will further investigate the role of OXTR+ ACC-BLA neurons in socially-motivated investigative behavior by performing in-vivo optogenetic activation of OXTR+ ACC-BLA neurons within middle-ranked mice undergoing a dual-choice assay. Finally, using viral tracing strategies, we are defining the presynaptic inputs to OXTR+ ACC-BLA neurons to fully characterize how OXTR+ ACC neurocircuitry may modulate the conversion of social information into emotional behaviors. Together, this work will provide a comprehensive view into how social olfactory information processed through the ACC-BLA circuit is shaped by oxytocin to drive different emotional behaviors.

Disclosures: B. Uceda-Alvarez: None. **E. Rodriguez:** None. **C. Adeyemi:** None. **H. Ibarra Avila:** None. **C. Lee-Kong:** None. **M. Thurnherr:** None. **C.D. Salzman:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.08/O26

Topic: G.03. Motivation

Support: KAKENHI 21J01636

Title: Auricular vagus nerve stimulation alleviates social deficits induced by adolescent social isolation or maternal immune activation in mice

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Abstract: The afferent vagal sensory nerve conveys information in peripheral organs to brain and vagus nerve signaling could modulate cognitive and emotional functions. The vagus nerve stimulation (VNS) has been developed as treatment for epilepsy and highlighted for positive effects on depression or other psychiatric disorders. Especially, transcutaneous auricular vagus nerve stimulation, which stimulates auricular branch of vagus sensory nerve, is developed as non-invasive methods for VNS and expected to be applied to various psychiatric disorders. In addition, recent animal studies have been reported that vagus nerve activation might modulate social behavior and it is possible that auricular VNS could be effective intervention for psychiatric disorders with social deficit such as ASD. However, it remains unclear whether auricular vagus stimulation modulates social behavior. Here, we examined the effect of auricular VNS on social deficit induced by adolescent social isolation or maternal immune activation in mice. For adolescent social isolation paradigm, weaned mice (3 week of age) were isolated from

other mice throughout adolescence and performed behavioral analysis after maturation (8-9 weeks of age). For maternal immune activation (MIA) paradigm, pregnant mice were injected with LPS at E12.5 and the pups were performed behavioral analysis after maturation. For auricular VNS, subjected mice were applied electrical stimulation to auricular concha area, which innervated area by vagus nerve branch. For sham stimulation, mice were stimulated auricular helix area, which is less innervated area by vagus nerve. Interestingly, acute auricular VNS alleviated the decrease of social preference in socially-isolated and MIA mice, but not sham stimulation. In addition, auricular VNS increased the number of c-Fos positive cells in the nucleus of solitary tract (NTS) and other brain regions involving social behavior, compared with sham stimulation. These data suggested that auricular VNS modulated social behavior through activation of the NTS and downstream social brain regions in mice.

Disclosures: H. Kuniishi: None. **H. Matsuzaki:** None. **M. Xie:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.09/O27

Topic: G.03. Motivation

Support: MSU Grant GR100606

Title: Does social play exposure reduce inflammatory pain? Investigating the interaction between social play and CFA-induced pain in juvenile male and female Wistar rats

Authors: *K. D. BECKER[1], G. O. LAUMET[2], A. H. VEENEMA[3];
[1]Michigan State Univ., East Lansing, MI; [2]Dept. of Physiol., Michigan State Univ., East Lansing, MI; [3]Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: The treatment of chronic pain is a major clinical problem affecting 50 million Americans, with pediatric pain remaining under-investigated and poorly managed. When hospitalized, children are bedridden and lose their ability to engage in social play with peers. Children need social play with peers for a healthy physical, emotional, and social development. However, the potential positive impact of social play exposure on disease outcomes remains largely unexplored. Thus, the current study explores the hypothesis that exposure to social play facilitates the resolution of pain. To test this, Wistar rats will receive a subcutaneous injection of Complete Freund's Adjuvant (CFA) or saline in the right hindpaw upon weaning at postnatal day 21 (P21). Rats will then be assigned randomly to the no play condition (socially isolated) or the free play condition (unlimited access to their non-litter cage mate to play with; the cage mate received the same injection). Over the next two weeks, the effects of social play exposure on CFA-induced pain will be assessed by measuring mechanical pain using the Von Frey filament test, and the effects of CFA on social play behavior will be assessed by analyzing social play behaviors. We predict that the free play CFA-treated rats will have a higher threshold for

mechanical pain than no play CFA-treated rats. We further predict that CFA will not affect social play behaviors. If we find effects of social play on CFA-induced pain or of CFA-induced pain on social play, we will obtain paw skin and brain tissue to explore the underlying mechanisms. Paw skin tissue will be used to assess the immune landscape using high-dimensional spectral flow cytometry. We predict that social play will reduce proinflammatory and increase anti-inflammatory molecules. Brain tissue will be analyzed using immunohistochemistry to determine social play and pain impact on the expression of social neuropeptides oxytocin and vasopressin. We predict to find higher oxytocin/vasopressin expression in the free play CFA-treated rats versus no play CFA-treated rats. This study will be a first step to reveal the impact of social play on chronic pain.

Disclosures: K.D. Becker: None. **G.O. Laumet:** None. **A.H. Veenema:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.10/O28

Topic: G.03. Motivation

Support: NIH Grant R01MH102456

Title: Regulation of social play by dopamine and oxytocin in the nucleus accumbens of juvenile male and female rats

Authors: *S. M. BOWDEN[1], K. BECKER[2], A. H. VEENEMA[2];
[1]Psychology, Michigan State Univ., East Lansing, MI; [2]Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: Social play is a motivated and rewarding behavior primarily displayed during the juvenile period of many mammalian species. Participation in social play aids in the development of social competency and flexibility while deficits in social play, as seen in autistic children, may contribute to life-long difficulties with social interactions. Additionally, autistic children find social interactions less pleasurable and are less motivated to seek out these social interactions. This indicates the need for research into the neural basis of the motivating and rewarding aspects of social play, which may lead to therapeutic strategies to improve social play engagement in autistic children. Here, we focused on the role of the nucleus accumbens (NAc) in social play behavior, as the NAc is involved in the regulation of motivated and rewarding behaviors. The NAc expresses the dopamine 1 receptor (D1R) and D2R, which have been shown to differentially modulate rewarding social behaviors in adult rodents. In addition, D1R and D2R expressing neurons co-express the OXTR. Interactions between D2R and OXTR in the NAc facilitate rewarding adult social behaviors such as pair bonding. The purpose of this study was to investigate the role of D1R, D2R, OXTR, and OXT in the NAc, as well as the potential interplay between OXT and DA receptor systems, on social play in juvenile male and female rats. Rats

were bilaterally cannulated in the NAc and infused with either a D1R antagonist, D2R antagonist, OXTR antagonist, or OXT 20 minutes prior to play testing. We found that D1R or OXTR antagonism did not alter juvenile social play in either sex. However, D2R antagonism decreased duration and frequency of social play behaviors in both males and females. Finally, infusion of OXT into the NAc decreased social play duration and frequency in males, while OXT infusion in females showed increased levels of social play compared to males. Together, this research demonstrates the necessity of D2R signaling and provides evidence for a sex-specific role of OXT in the NAc in the regulation of social play behavior. Current studies will determine whether infusion of OXT in the NAc following D2R antagonism may further modulate D2R antagonist mediated changes in juvenile social play. Overall, our findings may have implications for the need for sex-specific use of OXT-based and/or combinatorial treatment of OXT and DA to improve social play engagement in autistic children.

Disclosures: S.M. Bowden: None. **K. Becker:** None. **A.H. Veenema:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.11/O29

Topic: G.03. Motivation

Support: R00MH124435

Title: Context-dependent dopamine dynamics in medial prefrontal cortex and nucleus accumbens during social interactions and competition in mice

Authors: *A. LI, M. CUM, C. YE, N. PADILLA-COREANO;
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Abstract: Dopamine (DA), a critical neuromodulator involved in learning and motivated behaviors, has been associated with dominance behaviors. Past studies show that dominance behavior in rodents is associated with higher concentration of DA in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) (Couppis et al 2008; Lozano-Montes et al 2019). A recent study showed that DA in the NAc signals social motivation and positive valence during social interactions (Dai et al., 2022). DA signaling in the mPFC has a less clear role, with some studies showing DA activity linked to aversive stimuli while others show activity linked to attention, regardless of valence. (Vander Weele et al., 2018; Melugin et al., 2024). However, these past mPFC DA studies did not use social stimuli. We address this gap and investigate whether DA has circuit specific effects in the NAc and mPFC during social interactions in mice. Using dLight1.3b, we recorded DA fluorescent transients in the mPFC or NAc of C57BL6 mice during interactions with various social agents: novel, short-term familiar (10 minutes prior interaction with subject), long-term familiar (cagemate), and aggressor (CD-1). We also recorded mPFC or NAc DA during a social competition for rewards to investigate the role of DA in

dominance related behavior. Preliminary analysis suggests that mPFC DA responds more than NAc in aversive interactions with an aggressor mouse of a different strain. In addition, during social competition for rewards, DA dynamics differ in both regions depending on the competitive success of the mouse. This study will increase our understanding of how mesocortical and mesolimbic dopamine may shape social behaviors depending on context and valence of the interaction.

Disclosures: A. Li: None. **M. Cum:** None. **C. Ye:** None. **N. Padilla-Coreano:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.12/O30

Topic: G.03. Motivation

Support: NIMH Grant MH133123-01

Title: Opposite-sex pairing alters social interaction-induced GCaMP and dopamine activity in the insular cortex of male prairie voles

Authors: *E. VITALE[1], A. TBABA[2], K. TAM[1], A. S. SMITH[3];
[1]Univ. of Kansas, Lawrence, KS; [2]Pharmacol. and Toxicology, Univ. of Kansas, Lawrence, KS; [3]Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS

Abstract: The prairie vole (*Microtus ochrogaster*) is a monogamous rodent species that has been used to study the neurobiological mechanisms underlying the display of social behavior due to their formation of selective, opposite-sex relationships known as pair bonds. Pair bonding in males and females is determined behaviorally by selective affiliation for a social partner over other conspecifics and intruder-directed aggression. This social selectivity relies on the ability of an individual to respond appropriately to a social context and requires complex salience detection and valence assignment. The anterior insular cortex (aIC) has been implicated in stimulus processing and categorization across a variety of contexts. As a “higher-order” cortical region with unique afferent and efferent connections to sensory, visceral, and stress-related brain regions, it is well-situated to integrate complex environmental stimuli and internal affective states to modulate complex goal-directed behaviors and social decision-making. However, the contribution of this brain region to the formation and/or maintenance of pair bond-induced social selectivity in prairie voles has been drastically understudied. In this series of experiments, we sought to examine whether neural activity and gene expression in the aIC changes in response to opposite-sex pairing and/or as a function of pairing length in male prairie voles. We used fiber photometry to assess activity of a genetically encoded calcium indicator (GCaMP) and a fluorescent dopamine (DA) sensor ($GRAB_{DA}$) in response to familiar and novel social encounters in subjects housed with either a same-sex peer or an opposite-sex mate. We found that opposite-sex pairing is characterized by unique social proximity-induced GCaMP and DA

activity patterns in the aIC that appears to reflect changes in valence and salience processing of specific social encounters and relates to the display of social selectivity across pair bond maturation. Furthermore, opposite-sex pairing alters DA receptor mRNA expression within the aIC, such that D1 and D2 receptor expression becomes significantly positively correlated with one another. We are currently tracing and characterizing the projections from the prairie vole aIC to the mesocorticolimbic DA and examining whether it plays a functional role in the formation or maintenance of pair bonding and the expression of pair bond-induced social selectivity.

Disclosures: E. Vitale: None. **A. Tbaba:** None. **K. Tam:** None. **A.S. Smith:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.13/O31

Topic: G.03. Motivation

Support: MH119422

Title: Periaqueductal gray contributes to social approach and avoidance behaviors in rat

Authors: *A. J. NG, J. P. CHRISTIANSON;
Psychology & Neurosci., Boston Col., Chestnut Hill, MA

Abstract: The periaqueductal gray's (PAG) role in defensive behaviors, nociception, and pain is well understood, but less is known about its role in social affective behaviors. In an analysis of functional connectivity among regions involved in social behavior, we reported that PAG participation in the network varied depending on the age and affect (naive to stress vs. stressed) of the social target of the interaction. Therefore, we hypothesized that social affective behaviors towards stressed juvenile (PN30) and adult (PN60) conspecifics engage and require the PAG. To test this, we manipulated PAG activity pharmacologically or chemogenetically in adult male rats. First, we temporarily inactivated the PAG by directly administering the $GABA_A$ agonist muscimol (100ng/side) through bilateral cannula implanted in the PAG prior to a 5-minute social affective preference test. Muscimol administration prevented the approach of stressed PN30 conspecifics in the social affective preference test without affecting overall sociability (total interaction time). Next, we infused pAAV5-hSyn-hM4D(Gi)-mCherry bilaterally into the PAG to chemogenetically inhibit PAG activity. 3 weeks after infusion, intraperitoneal (i.p.) administration of the hM4D(Gi) ligand deschloroclozapine (DCZ, 0.1mg/kg) prevented the approach and avoidance, respectively, of stressed PN30 or stressed PN60 conspecifics in a social preference test without affecting overall sociability. In a sex preference test, DCZ administration did not influence preference to approach the female conspecific, suggesting the PAG is involved in more nuanced social decision-making. The PAG is innervated by the insular cortex, which is also critical to social affective behaviors. Ongoing studies using intersectional viral genetic manipulations will characterize the subregions and cells of the PAG that are postsynaptic to

insular afferents and determine whether an insular-PAG circuit is necessary for social affective behaviors.

Disclosures: A.J. Ng: None. **J.P. Christianson:** None.

Poster

PSTR479: Motivation: Social Communication and Behavior II

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR479.14/O32

Topic: G.03. Motivation

Support: NIH Grant MH119422

Title: An anterior insular cortex - prelimbic cortex circuit mediates social affective preference in rats

Authors: *E. CHUN[1], A. DJERDJAJ[2], T. MATULIS[1], A. J. NG[3], J. P. CHRISTIANSON[3]; [1]Boston Col., Chestnut Hill, MA; [2]Psychology, Boston Col., Chestnut Hill, MA; [3]Psychology & Neurosci., Boston Col., Chestnut Hill, MA

Abstract: In order to safely navigate the social world, animals must be able to adjust their behavior in response to information derived from conspecifics. The integration of social information and orchestration of social interactions are mediated, in part, a distributed social decision making network. The prelimbic (PL) region and the anterior insula (aIC) are anatomically and functionally connected to the social decision making network and are implicated in social behavior. We investigated the aIC-PL circuit in mediating social affective preference (SAP) behavior - a test in which subject rats are exposed to two age-matched conspecifics where one is stressed via footshock and the other is naive to stress. Typically, rats approach stressed juvenile conspecifics but avoid stressed adults. In three experiments, we examined the role of the aIC-PL in SAP behavior by using an inhibitory chemogenetic strategy. First, chemogenetic inhibition of the aIC itself in rats with bilateral aIC injections of pAAV5-hSyn-hM4D(Gi)-mCherry abolished preference for stressed juveniles and naive adults. Next, using a combination of anterograde and retrograde tracing, we demonstrate robust connectivity between the aIC and the PL, with aIC inputs making synaptic connections with primarily glutamatergic PL neurons. Inhibition of PL neurons postsynaptic to aIC input in rats with anterograde AAV1-hSyn-Cre deposited in the aIC and AAV5-DIO-hM4Di into the PL, disrupted typical social affective preference by decreasing preference for stressed juveniles and for naive adults. Ongoing studies using chemogenetic inhibition of aIC terminals in the PL will test the hypothesis that aIC input to the PL is necessary for social response to stressed conspecifics. These studies enrich our understanding of the neurobiology of social decision making by establishing a mechanistic link between insular and prefrontal circuits.

Disclosures: E. Chun: None. **A. Djerdjaj:** None. **T. Matulis:** None. **A.J. Ng:** None. **J.P. Christianson:** None.

Poster

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Program #/Poster #: PSTR479.15/O33

Topic: G.03. Motivation

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The Helen Hay Whitney Foundation
NIMH Grant T32MH015144

Title: Examining a cortico-amygdala pathway in sexually-dimorphic olfactory-guided social motivation

Authors: *E. RODRIGUEZ[1], B. UCEDA-ALVAREZ[1], R. NGUYEN[1], C. ADEYEMI[1], E. J. KYZAR[2], C. LEE-KONG[1], M. THURNHERR[1], C. D. SALZMAN[1,3,4];
[1]Zuckerman Inst., Columbia Univ., New York, NY; [2]Psychiatry, Columbia Univ., New York, NY; [3]Neuroscience, Columbia University, New York, NY; [4]Psychiatry, Columbia University, New York, NY

Abstract: Social interactions have a profound impact on the way we think, feel, and make decisions, thereby shaping our emotional and motivational behavior. This process occurs through neural mechanisms that represent sensory information about social agents to identify them, and that then assign meaning to social stimuli. However, we lack detailed mechanistic insight into how the brain represents, integrates, and converts social information into meaningful signals that exert effects on emotional processing, motivation, and decision-making. Our work focuses on how the important social construct of hierarchy modulates emotional and motivational behavior and whether this is sexually dimorphic in mice. Previous work has shown that the anterior cingulate cortex (ACC) and basolateral amygdala (BLA) play a role in processing emotional and social information. We therefore sought to examine whether the ACC-BLA pathway is necessary for the processing and conversion of social olfactory information related to social hierarchy into motivated behavior. To address this question, I developed an approach which incorporates an infrared beam-break assay with well-controlled social olfactory stimuli from dominant and submissive mice, allowing us to activate and visualize brain regions involved in social sensory processing and investigate how these regions drive motivational behavior in middle-ranked mice. Measuring approach behavior and orientation, we found that male mice investigated dominant odors more than submissive odors, and the inverse was seen in female mice. Using a closed-loop optogenetic silencing strategy, we found that the ACC-BLA pathway is necessary for this rank-dependent and sex-specific motivational behavior. Leveraging molecular and cellular tools, we are currently examining the population dynamics of ACC neurons with projection- and cell-type specificity during socially-driven motivational behavior. These analyses will reveal how social sensory information is sequentially processed in the ACC, resulting in differential motivational behavior that is sexually-dimorphic. Overall, these investigations will provide fundamental mechanistic insights to target critical points within the sensory- and emotional-processing

circuits. In the future, we plan to use these insights to study how neural processing becomes dysfunctional in mouse models of psychiatric disorders, potentially providing points of leverage for developing new treatment strategies.

Disclosures: E. Rodriguez: None. **B. Uceda-Alvarez:** None. **R. Nguyen:** None. **C. Adeyemi:** None. **E.J. Kyzar:** None. **C. Lee-Kong:** None. **M. Thurnherr:** None. **C.D. Salzman:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.01/O34

Topic: G.04. Emotion

Title: A dedicated LC-NAergic system distinguishes vicarious versus direct fear in mice.

Authors: *J.-H. KIM[1], H.-S. SHIN[2];
[1]Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Seoul, Korea, Republic of

Abstract: Fear can be induced either directly by self-experience of aversive events or vicariously through social observation of conspecifics suffering from aversive events. The anterior cingulate cortex (ACC), a key region in vicarious fear responses as demonstrated in observational fear (OF), receives afferent signals from diverse regions including the locus coeruleus-noradrenaline (LC-NA) system. The LC-NA system plays critical roles in various brain functions, such as arousal, attention, cognition, memory, and fear response. However, the role of the LC-NA system in the diverse fear responses remains unknown. By utilizing optogenetics, photometry recording, and retrograde tracing, we demonstrate that the ACC-projecting LC-NA system in the right hemisphere supports the maintenance of OF. Through monosynaptic rabies tracing, the bed nucleus of the stria terminalis (BNST) and the central amygdala (CeA), both fear-related regions, were identified as the primary upstream inputs to the LC-ACC circuit. Either selective inhibition of the BNST-LC-ACC or general inhibition of the BNST-LC suppressed OF. Interestingly, a similar selective inhibition of the CeA-LC-ACC did not affect any fear response, vicarious or direct, whereas general inhibition of the CeA-LC suppressed fear responses in general through projections to BLA. This work provides new insights into a unique and specific LC-NAergic system dedicated to regulating vicarious fear distinguished from direct fear.

Disclosures: J. Kim: None. **H. Shin:** None.

Poster

PSTR480: Fear and Threat Representations

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Topic: G.04. Emotion

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VA Gant BX005642
CWRU funds

Title: An insular-amygdala circuit gates familiarity-dependent observational fear

Authors: *W.-J. ZOU, M.-Y. WU, W.-C. XIONG, L. MEI;
Neurosci., Case Western Reserve Univ., Cleveland, OH

Abstract: Empathy is the ability to attune to and resonate with the emotional states of others, indispensable for social communication. Deficits in empathic responsiveness are a hallmark feature of autism spectrum disorders (ASD). However, the exact mechanisms of empathy are not fully understood. Observational fear, which encompasses the mice (observers) acquiring freezing behavior by observing other mice (demonstrators) subjecting repetitive foot shocks, is a powerful tool for examining affective empathy in rodents. Here, we found that observer male mice exhibited heightened fear responses specifically toward their cagemate siblings and non-littermate cagemates demonstrator male mice, whereas they did not display elevated fear towards strangers or even non-cohabiting sibling mice. These findings illustrate that mice displayed familiarity-dependent observational fear irrespective of their genetic relatedness, suggesting that factors beyond mere emotional contagion may be involved in the process of observational fear learning. This elevation can be prompted by olfactory signals emanating from stressed co-house conspecifics. This suggests that olfactory cues released by stressed co-house conspecifics may act as mediators in the social transmission of fear in rodents. By conducting a thorough brain-wide histological investigation and employing projection-specific optogenetic manipulation, we identified an insular cortex (IC)-basolateral amygdala (BLA) circuit that selectively contributed to the familiarity-dependent observational fear. These findings illustrate that bidirectional manipulation of activity in the IC-BLA pathway plays a critical role in shaping the acquisition of familiarity-dependent observational fear, without affecting the general expression of observational fear. This suggests a potential causal link between IC-BLA activity and familiarity-dependent observational fear. Using a mouse model of mimics a common genetic factor to ASD—a de novo mutation of Cullin 3 (Cul3)—Cul3 mt mice exhibited compromised familiarity-dependent observational fear, characterized by decreased firing activity of IC-BLA neurons and diminished glutamatergic transmission. Together, our study demonstrates that mice exhibited familiarity-dependent observational fear regardless of kinship, highlighting the potential for targeted modulation of specific insular circuits may offer valuable prospects for ASD associated with empathy impairment treatment.

Disclosures: W. Zou: None. **M. Wu:** None. **W. Xiong:** None. **L. Mei:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.03/O36

Topic: G.04. Emotion

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107-2320-B-002-040-MY3
108-2638-B-010-0020-MY2
110-2320-B-002-013-MY3
110-2321-B-010-006

Title: Investigation of efferent projections of the parabrachial nucleus

Authors: *S.-R. LEE, H.-H. LIN, H.-J. YAU;
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Abstract: The parabrachial nucleus (PBN) is known to regulate the feeding system and convey negative information. It is crucial to know how the PBN processes the incoming stimuli and recruits its efferent projections to drive adaptive behaviors. In the present study, we first examined the functional role of the PBN projection to the ventral tegmental area (VTA), a heterogeneous brain region that regulates motivational behaviors. By combining c-Fos immunostaining with a dual-viral tracing technique to specifically label active VTA-projecting PBN cells under different behavior paradigms, we found that these cells were significantly activated by negative emotions, such as stress, anxiety or contextual fear, but not thermal pain, vesicular malaise and palatable feeding. To further examine the sufficient role of PBN-recruited VTA neurons in feeding regulation, we combined an activity-dependent targeting approach with a dual-color optogenetic strategy to allow independently excite PBN-to-VTA inputs and PBN-recruited postsynaptic VTA neurons. We found that both excitatory optogenetic manipulations resulted in aversion, dampened freely palatable feeding and disturbed instrumental food-seeking behavior in a food self-administration task. The cellular phenotyping and projection mapping results further showed that PBN afferent activation mostly recruited VTA non-dopamine cells, which sent dense projections to the dorsal raphe nucleus (DR), lateral preoptic area (LPO), and peduncular part of the lateral hypothalamus (PLH), but not nucleus accumbens (NAc). These results support those negative emotions engage PBN and recruit VTA non-dopamine cells to convey negative valence and disengage food-seeking behavior.
In addition to the VTA, we also found that PBN sent prominent projections to the paraventricular nucleus of the thalamus (PVT), which is known to encode the salience of external stimuli and integrate with internal states, and serve as a modulator in sequencing adaptive behaviors. We utilized *in vivo* calcium imaging to specifically investigate the information encoded in the anterior part of the PVT (aPVT). We found that some aPVT cells were activated by stimuli associated with both positive (male and female conspecifics) and negative (predator-like odor, fear-associated cues) valence, as well as salient auditory cues. Interestingly, we also observed differential responses of aPVT cells to various types of diets, including chow diet, palatable food and high-fat diet during food consumption. Further calcium imaging experiments in a pathway-

specific manner will be required to help understand the functional roles of the PBN efferent projection to the aPVT.

Disclosures: S. Lee: None. **H. Lin:** None. **H. Yau:** None.

Poster

PSTR480: Fear and Threat Representations

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National Institute of Mental Health Grant MH002950 (M.A.P.).
NIMH IRP Rodent Behavioral Core (MH002952)

Title: The paraventricular nucleus of thalamus conveys aversive information to the central circadian clock

Authors: *M. E. YURGEL[1], C. GAO[2], N. YANAY[5], J. O'MALLEY[3], J. ZHAN[7], A. BASHFORD[8], H. ZHAO[9], M. A. PENZO[4], S. HATTAR[6];
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Abstract: Stressors reprogram animal behavior, enabling for the anticipation and response to environmental threats. Although the circadian system plays a central role in anticipating environmental changes, the effects of stressors on circadian rhythms are understudied. Here we show that stressors reprogram the suprachiasmatic nucleus (SCN) central circadian clock via glutamatergic inputs from the paraventricular nucleus of the thalamus (PVT). Fiber photometry recordings reveal that footshocks directly activate but also inhibit SCN neurons across the day. The delayed inhibition results from a feedforward inhibitory mechanism. Aversive stimuli phase delays the central circadian clock and silencing PVT neurons attenuates stress-induced delays. In addition, combining light and footshocks enhances phase delays in locomotor activity. Consistent with the enhanced phase delays, SCN neuronal responses to light and footshocks result solely in activation, without any inhibition. These findings show that the clock responds to stressors via a PVT-SCN pathway and integrates multiple cues for an accurate circadian response.

Disclosures: M.E. Yurgel: None. **C. Gao:** None. **N. Yanay:** None. **J. O'Malley:** None. **J. Zhan:** None. **A. Bashford:** None. **H. Zhao:** None. **M.A. Penzo:** None. **S. Hattar:** None.

Poster

PSTR480: Fear and Threat Representations

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Program #/Poster #: PSTR480.05/P1

Topic: G.04. Emotion

Support: JSPS Grant JP23H02640
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Title: Brain-wide circuit mapping of stress-related neuronal populations in the claustrum

Authors: Y. YOKOYAMA[1], M. TANUMA[1], J. OHKUBO[1], H. UENO[1], K. SEIRIKI[1], H. HASHIMOTO[1], ***A. KASAI**[2,1];
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Abstract: A subpopulation of neurons in the claustrum (CLA ensemble) mediates anxiety responses to acute psychological stressors that elicit negative emotional states and/or heightened vigilance. The CLA receives stress-related information from areas such as the medial prefrontal cortex and basolateral amygdala, but it remains unclear where CLA ensemble transmits this anxiety-related information. To address this question, we conducted circuit mapping of the CLA ensemble by labeling axon using adeno-associated virus (AAV) vectors. We injected AAV vectors (AAVdj-iCre, AAV9-ihSyn-DIO-tTA, and AAV9-TRE-membrane-targeting mScarlet) into the CLA and performed whole-brain imaging in mice. We found that the CLA ensemble predominantly projects ipsilaterally within the cortex and strongly projects to the deep layers of the perirhinal and entorhinal cortices, which are involved in spatial information processing, as well as to the cingulate cortex, which is involved in the emotional and social cognitive processing. These results suggest that the stress-related CLA ensemble may regulate these processes.

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Poster

PSTR480: Fear and Threat Representations

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Program #/Poster #: PSTR480.06/P2

Topic: G.04. Emotion

Support: NIMH R01-111604
NIAID R01-168014
NIMH R01- 121829

Title: Androgen receptors in vHPC projecting neurons to NAc regulates sex-specific responses to stress

Authors: *I. LAKIC[1], L. FURLETTI SANTIAGO[2], S. PILLAI[2], E. S. WILLIAMS[2], R. M. BASTLE[3], I. S. MAZE[4], A. ROBISON[5];
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Abstract: Androgen Receptors in vHPC projection neurons to NAc regulates sex-specific response to stress
Authors: Ivana Lakic, Elizabeth Williams, Ryan Bastle, Ian Maze, AJ Robison
Depression is a leading cause of disability in the United States and is nearly twice as prevalent in females as it is in males, but the molecular underpinnings of this discrepancy remain unclear. We previously showed that female mice have higher baseline excitability in ventral hippocampal (vHPC) neurons projecting to the nucleus accumbens (NAc), and that this higher excitability drives susceptibility to stress-induced anhedonic behavior (Williams et al., *Biol Psych*, 2020). This work also showed that the sex differences in both excitability and anhedonic responses to stress are dependent on adult testosterone, but the mechanisms of these testosterone effects are unknown. Neurons in the vHPC express high levels of androgen receptor (AR), and the present study examined whether testosterone-mediated resilience to stress-induced anhedonia in mice is dependent on AR activation specifically in the vHPC-NAc circuit. Using a novel intersecting viral strategy, we knocked out AR expression specifically in vHPC cells projecting to NAc in transgenic Cre-inducible Rosa-eGFP-L10a male mice floxxed for AR, then exposed them to chronic unpredictable stress (CUS). We then used a battery of behavioral tests to examine the role of vHPC-NAc AR expression in responses to stress, including sucrose preference as a measure of anhedona. Circuit-specific AR knockout was validated using dual label immunofluorescence. Our results show that knocking out the AR in vHPC-NAc projecting neurons increased susceptibility to stress-induced behavioral changes in male mice demonstrated by a reduction in sucrose preference. We then examined whether testosterone-driven resilience in female mice is driven by AR signaling in vHPC-NAc neurons. Both ovariectomized and non-ovariectomized female mice were implanted with either placebo, testosterone, or dihydroxy-testosterone (DHT) pellet for 21 days. We hypothesize that treatment with DHT will have no pro-resilient effect in ovariectomized vHPC-NAc AR^{KO} females compared to their AR intact controls. Taken together, these data indicate that testosterone acts through ARs on vHPC-NAc neurons to reduce excitability and convey resilience to anhedonia, providing insight for future sex-specific therapeutic intervention in depression disorders.
Keywords: stress, depression, androgen receptor, sex differences, nucleus accumbens, ventral hippocampus

Disclosures: I. Lakic: None. **L. Furletti Santiago:** None. **S. Pillai:** None. **E.S. Williams:** None. **R.M. Bastle:** None. **I.S. Maze:** None. **A. Robison:** None.

Poster

PSTR480: Fear and Threat Representations

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Program #/Poster #: PSTR480.07/P3

Topic: G.04. Emotion

Support: NIMH R01-111604
NIAID R01-168014
NIMH R01- 121829

Title: Role of testosterone presence in ventral hippocampus immediately prior to stress exposure in priming neurons for stress-resilient response

Authors: *L. FURLETTI SANTIAGO[1], S. PILLAI[1], I. LAKIC[2], A. ROBISON[3];
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[3]Physiol., Michigan State Univ., Okemos, MI

Abstract: Role of testosterone in ventral hippocampus immediately prior to stress exposure in priming neurons for stress-resilient responses
Authors: Laura Furletti Santiago, Shruthi Pillai, Ivana Lakic, AJ Robison
Major Depressive Disorder (MDD) affects around 8% of the population in the US, with 30-50% of individuals not responding to treatment. Additionally, a two-fold higher prevalence of MDD is seen in females when compared to males; however, the molecular mechanisms of this sex difference are still unclear. Chronic stress is a leading cause of depression, resulting in a dysregulation of glutamatergic signaling in brain regions associated with reward and motived behavior, specifically in glutamatergic vHPC (ventral hippocampus) neurons projecting to the NAc (nucleus accumbens). In addition to its role in mediating stress responses, the vHPC is a sexually dysmorphic region with high expression of both androgen (AR) and estrogen sex hormone receptors. Previously, our lab has shown that lower vHPC-NAc excitability in male mice drives resilience to stress-induced anhedonia whereas higher excitability was seen in females, driving susceptibility (Williams et al., 2020). Additionally, we observed that knocking out ARs specifically in vHPC-NAc projecting neurons resulted in increased susceptibility to anhedonia in male mice. Studies have also shown that sex hormone presence in the brain immediately before stress exposure primed neurons for sex-specific responses to stress. Thus, this study examines whether injection of the potent androgen, dihydrotestosterone (DHT), prior to stress increases the expression of stress-resilient genes in the vHPC in male and female mice. To test this, we administered wild type male and female mice with DHT one hour prior to stress, and immediately following stress exposure, mice were euthanized and vHPC tissue was collected. To determine whether gene expression changes following DHT administration were specific to an AR-mediated pathway, we knocked out the AR through a novel intersecting viral strategy in transgenic Cre-inducible Rosa-eGFP-L10a male and female mice AR floxxed mice to specifically knock out receptors in the vHPC neurons projecting to the NAc. Finally, in order to examine whether the protective effects of testosterone are long-lasting, we extended the DHT treatment for five consecutive days. This study may provide a better understanding of how testosterone and ARs modulate stress response and will provide us with insight into the

molecular mechanisms of sex-specific responses to stress relevant to depression.
Keywords: stress, depression, testosterone, sex differences, ventral hippocampus, gene expression

Disclosures: L. Furletti Santiago: None. **S. Pillai:** None. **I. Lakic:** None. **A. Robison:** None.

Poster

PSTR480: Fear and Threat Representations

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Guangdong Basic and Applied Basic Research Foundation (2023B1515040019 to BL)
Guangdong Project (2017GC010590 to BL)

Title: Sexually dimorphic cortical circuits mediate sex-specific empathic behaviors

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Abstract: Empathy, the capacity to understand others' sensory or emotional state, plays a critical role in social communication. It is widely acknowledged that males and females may display different empathic responses toward the same social situation; however, the neural mechanisms underlying sex differences in empathy are largely unknown. Here we report that sexually dimorphic activation of neuronal populations and circuits in the piriform cortex (PiC) is essential for sex differences in empathy. Specifically, when witnessing a cagemate experiencing pain, female mice activate the PiC to the prelimbic cortex (PrL) pathway to mediate social preference for the cagemate in pain. In contrast, male mice activate the PiC to the medial amygdala (MeA) pathway to display excessive self-grooming. Neural circuit tracing and transcriptomic analysis revealed that the two pathways originate from two non-overlapping populations of PiC neurons with distinct transcription factor- and sex hormones-regulated gene expression signatures. These results indicate that sex differences in empathy are controlled by sexually dimorphic mechanisms at the molecular, cellular, and circuit levels. They also provide a framework for understanding the neural mechanisms underlying the deficits of empathy in many neuropsychiatric disorders.

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Poster

PSTR480: Fear and Threat Representations

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Topic: G.04. Emotion

Support: Start-up funds from Johns Hopkins University (HA and SPM)

Title: Modulation of exploratory-avoidant behaviors by mPFC-projecting BLA neurons

Authors: *H. HUANG[1], G. SHAH[2], S. P. MYSORE[2], H. ADWANIKAR[3];
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Abstract: The basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are known to modulate exploratory-avoidant behaviors. The BLA plays a pivotal role in interpreting the emotional valence of external stimuli, forwarding this information via diverse pathways, with the medial prefrontal cortex (mPFC) being a prominent target. The mPFC receives and evaluates cues from the BLA (as well as behaviorally relevant contextual information from the ventral hippocampus (vHPC)), and provides feedback to downstream regions including BLA, striatum, and nucleus accumbens, to either enable or suppress avoidant responses. Consequently, BLA projections to the mPFC are implicated in coding aversive cues and have been shown to modulate behavior in exploratory-avoidant tasks. However, the broader functional role of mPFC-projecting BLA neurons in exploratory-avoidant behaviors remains unclear. Here, we addressed this question using a projection-defined chemogenetic approach in mice engaged in a classic exploratory-avoidant task, namely, the elevated zero maze (EZM) task. We injected a retroAAV encoding for cre-recombinase in the mPFC and cre-dependent inhibitory DREADD hM4Di in the BLA neurons. This allowed us to selectively inhibit mPFC-projecting BLA neurons by administering the designer drug CNO 30 min prior to the task. Saline injection served as a control. To additionally account for the potential impact of repeated exposure to the EZM, we ran a separate cohort of animals on the EZM and compared their behaviors at multiple time points corresponding to the experimental conditions with CNO/saline. We found that inhibiting mPFC-projecting BLA neurons (with CNO injections) promoted avoidant behaviors. Notably, this effect could not be attributed to the effects of injection or repeated maze exposure. Surprisingly, these findings are directly opposed to findings from previous work that suppressed BLA projection fibers in the mPFC. The contrasting results from cell-body versus axonal manipulations of the same mPFC-projecting BLA neurons suggest complex, pathway-dependent roles for this subgroup of BLA neurons in exploratory-avoidant behavior. Additionally, our results also provide guidance for future experimental designs involving repeated exposure to the EZM.

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Poster

PSTR480: Fear and Threat Representations

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Program #/Poster #: PSTR480.10/P6

Topic: G.04. Emotion

Support: NIMH Intramural Research Program

Title: The role of the macaque amygdala in detecting predator targets in a conceptual oddity task

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Section on Neurobio. of Learning and Memory, Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract: Macaques exhibit defensive responses in the presence of real or fake snakes; the expression of these defensive responses depends on the integrity of the amygdala (Izquierdo et al., *J Neurosci* 2005). Because macaques have been reported to have a reaction time (RT) advantage in identifying snake targets in the context of visual oddity tasks (Kawai and Koda, *J Comp Psychol* 2016), this suggests the possibility that the amygdala may be mediating enhanced predator detection in addition to mediating defensive responses. To test this idea, we trained adult male rhesus monkeys (*Macaca mulatta*) with bilateral neurotoxic lesions of the amygdala (N=3) and unoperated controls (N=4) on a conceptual oddity task in which a target image (the odd-one-out) should be selected among distractor images from another category. On each trial, nine different images were presented in a 3 x 3 grid on a touch-sensitive screen. One of the images was the target; the other eight were distractors. If the target was selected, a sucrose pellet was delivered; if a distractor was selected, no food was delivered. Either event led to initiation of the intertrial interval. Two experiments were performed with different target-distractor composition. In Experiment 1, the target was either a snake image or a fish image presented against flower images. The snake- and fish-target trials were interleaved pseudorandomly. In Experiment 2, the two categories, snake and fish, served as target and distractor against each other. This was carried out in blocks; after 6 sessions (432 trials) involving one category as the target, they switched roles and then another 6 sessions were run. We analyzed the effects of the target type (snake, fish) and group (amygdala lesion, control) on the RT with 2-way ANOVAs. The RTs were significantly different between snake and fish targets in both experiments, but the direction was opposite. In Experiment 1, the RT to the snakes was faster (p<0.01) and, in Experiment 2, the RT to the fishes was (p<0.001). The RT of monkeys with amygdala lesions was slower in both experiments (p<0.05 and p<0.001, respectively). No significant interaction of group and target type was found in either experiment. However, an analysis of within-subject differences in RT revealed a significant effect of the amygdala lesion. The differences in the RTs to the snake versus fish targets in Experiment 1 were smaller in the lesion group (p<0.05). Thus, there was evidence for an attenuation of the enhancement of snake-target selection in monkeys with amygdala lesions. These results indicate that the amygdala plays an essential role not only in generating defensive responses to snakes, but also in prioritizing their visual search.

Disclosures: J. Hwang: None. **P.L. Noble:** None. **E.A. Murray:** None.

Poster

PSTR480: Fear and Threat Representations

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Topic: G.04. Emotion

Support: NINDS R34NS122050

Title: The organization of single-neuron projections from basolateral amygdala neurons to temporal lobe and subcortical structures in macaque

Authors: *K. CRAWFORD[1], Z. R. ZEISLER[2], M. A. ELDRIDGE[3], E. A. MURRAY[4], P. H. RUDEBECK[2];
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Abstract: The amygdala is involved in several aspects of cognition, including social cognition, reward processing, affect, salience, and motivation. One critical role for the amygdala is to influence the processing of emotionally salient stimuli, such as faces. Some of the strongest projections from the basolateral amygdala (BLA, comprised of the lateral, basal and accessory nuclei) are to temporal lobe structures. We hypothesize that these connections are responsible for influencing the processing of emotionally salient stimuli. The structure and organization of the connections from BLA to the temporal lobe at the level of single neurons is, however, unknown. One possibility is that individual neurons in BLA branch and send collaterals to multiple parts of the temporal cortex. Axonal branching allows information to be sent synchronously to multiple brain regions. For example, branching could be how neurons in BLA simultaneously influence processing at multiple points along the ventral visual stream. The recent application of multiplexed analysis of projections by sequencing (MAPseq) in macaques means that we now have a viable method to study single neuron projections in the brain, at scale, by using barcoded mRNA. To determine the patterns of anatomical projections of single BLA neurons to the temporal lobe in rhesus macaques we injected barcoded sindbis virus into BLA and dissected regions of interest spanning the length of the temporal cortex. We then assessed the patterns of single neuron projections to temporal cortex, as well as the degree to which single BLA neurons projected to both temporal and frontal lobes. Our preliminary data indicate that BLA neurons that project to either the entorhinal cortex or hippocampus are also likely to project to parts of the frontal lobe, such as parts of orbital and subcallosal anterior cingulate cortex. Additionally, BLA neurons that project to the entorhinal cortex are also likely to project to the hippocampus. This indicates that BLA neurons not only project to multiple locations in the temporal lobe but also innervate multiple lobes in the brain. Further analyses will concentrate on revealing the single neuron connections to parts of the temporal lobe that receive extensive innervation from amygdala, especially the densely innervated temporal pole areas. These analyses will help to

provide a potential anatomical basis for how single neurons in the amygdala influence the processing of emotionally salient stimuli across multiple parts of the temporal lobe.

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Poster

PSTR480: Fear and Threat Representations

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Program #/Poster #: PSTR480.12/P8

Topic: G.04. Emotion

Support: NIMH K01MH123783

Title: The representational geometry of emotion states in basolateral amygdala

Authors: *P.-K. O'NEILL[1], L. POSANI[2], J. MESZAROS[1], C. E. SCHOONOVER[3], A. P. FINK[1], S. FUSI[4], C. D. SALZMAN[2];
[1]Columbia Univ., New York, NY; [2]Zuckerman Inst., Columbia Univ., new york, NY; [3]Neurosci., Columbia Univ., New York, NY; [4]Univ. of Bern, Bern, Switzerland

Abstract: Emotional responses to salient events can generate multiple behaviors, such as freezing and fleeing in response to threat. We asked how the basolateral amygdala, a key brain structure involved connecting emotionally relevant stimuli to behavior, encodes 1) external stimuli, 2) their associated emotional valence, and 3) the behavioral states mice produce that reflect emotion states. To investigate these questions, we placed mice in a virtual burrow in which they display two distinct defensive behaviors including trembling (freezing) and ingressing (fleeing) to safety. A precise measurement of ongoing behavior alongside simultaneous two-photon calcium imaging of single neuron activity in BLA enabled us to probe how neural populations encode all of these variables.

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Poster

PSTR480: Fear and Threat Representations

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Topic: G.04. Emotion

Support: NIH Vision Sciences Training Grant (T32EY013933)

Title: The Neural Representation of Valence, Intensity, and Other Emotional Variables in Primate Amygdala, IT, and Insula

Authors: *R. HASHIM[1], R. A. GULLI[2], W. J. JOHNSTON[2], S. FUSI[2], C. D. SALZMAN[2,3]; [2]Zuckerman Inst., [1]Columbia Univ., New York, NY; [3]New York Psychiatric Inst., New York, NY

Abstract: The circumplex model of affect, formalized by James Russel in the early 1980s, describes a spatial model in which affective states are products of two independent neurophysiological systems — the valence circuitry and the arousal/intensity circuitry. To test this theory experimentally, we have trained monkeys to perform a mixed appetitive-aversive reversal learning task whereby 4 conditioned stimuli (CS) appear, each paired after a trace interval with a different unconditioned stimulus (US; large or small aversive air-puff or liquid reward). The magnitude and/or probability of reinforcement determines US intensity. CS-US contingencies reverse without warning, creating 8 unique trial conditions. New stimuli are generated each experiment, requiring monkeys to learn novel CS-US associations each day. We assay monkeys' learning of these associations using measures of anticipatory blinking and licking, as well as analyses of video data of a monkey's face and body. Further, to track revealed preferences during learning, we randomly interleave choice trials in which two fractals are presented simultaneously and the trial's US is determined by fixation on one of the fractals. Analyses of behavioral data on our task demonstrate that we can accurately predict the valence, intensity, and identity of the CS presented using linear decoders on the combined behavioral data taken from the trace interval prior to reinforcement. In neurophysiological experiments, we are employing NHP Neuropixels to simultaneously record from amygdala, IT, and insula while monkeys perform the reversal learning task. We are using analyses of the geometry of the neural representation in these areas to describe the computational capabilities of neural ensembles. In particular, we test 4 major hypotheses: 1) stimulus intensity and valence are represented by orthogonal coding directions, which would confirm a key aspect of the circumplex model; 2) the representations of stimulus valence and intensity each is low-dimensional, potentially enabling emotional generalization across conditions; 3) despite representing some variables with lower-dimensional structure, stimulus identity is still represented, facilitating readouts that are specific to particular stimuli; and 4) a comparison of the relative timing as a function of time and trial number across brain areas reveals the distinctive contribution of each recorded brain structure to computations relevant to the learning and expression of behaviors that emotional states elicited by the different conditioned stimuli.

Disclosures: R. Hashim: None. **R.A. Gulli:** None. **W.J. Johnston:** None. **S. Fusi:** None. **C.D. Salzman:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.14/P10

Topic: G.01. Fear and Aversive Learning and Memory

Support: NSF/IOS 1924732
NIH R01MH123260-01

Title: Prelimbic cortex representations of valence across time

Authors: *R. L. BACKSTROM[1], M. R. LOPEZ[2], M. E. NORMANDIN[3], P. M. OGALLAR[4], S. H. WASBERG[1], I. MUZZIO[5];
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Abstract: Anxiety disorders are the most common mental illnesses among Americans, affecting about 40 million adults every year. A hallmark of anxiety disorders, like PTSD, is an inappropriate pattern of generalization and discrimination in response to “safe” and “unsafe” stimuli. Since these disorders persist years after the original threats have been encountered, the development of treatments must consider not only the neural mechanisms underlying the encoding of emotional memories, but also their consolidation at remote time points. Memories are initially formed and consolidated in subcortical regions, followed by information transfer and consolidation in neocortical areas. Recent evidence supports the involvement of the prelimbic cortex (PL) in early and remote memory consolidation. While recent memory traces are thought to be relatively unstable, the stability of remote traces is debated. Specifically, when reorganization of memory traces occur and how this reorganization influences recall is unclear. In this study, we investigated if excitatory PL neurons display sound-evoked emotional representations of distinct valence and established if neural responses showed neural correlates of discrimination/generalization. Additionally, we assessed if neuronal ensembles that are active during retrieval stabilize or are continuously dynamic over time. Finally, we evaluated whether ensemble stability influences distinct aspects of memory during retrieval. Male and female mice were trained in a discriminatory fear paradigm, exposed to a tone paired with a foot-shock (CS+) and a tone never paired with a shock (CS-). On recent, long-term, and remote memory test days, the mice were exposed to two novel, intermediate tones, in addition to the CS+ and CS-. Using in vivo calcium imaging, we collected PL neural data and behavioral freezing data on all test days. Mice generalized fear to the intermediate tone similar to the CS+ and discriminated the tone similar to the CS- as safe. The population neural data mirrored these results, showing that PL neurons represented the valence of the tone stimuli, displaying proper discrimination/generalization. Tracking the activity of cells across the testing days, we found that the active ensembles were dynamic; however, there was a percentage of consistently active neurons. These neurons showed the same discrimination/generalization clustering pattern seen at the behavioral level, while the temporarily active cells did not. In the future, we aim to discover how the ability to discriminate/generalize properly is affected by chronic stress, on a behavioral and cellular level.

Disclosures: R.L. Backstrom: None. **M.R. Lopez:** None. **M.E. Normandin:** None. **P.M. Ogallar:** None. **S.H. Wasberg:** None. **I. Muzzio:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

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Program #/Poster #: PSTR480.15/P11

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIAAA Intramural Research Program

Title: Astrocytes enable neuronal representations supporting fear memory

Authors: *O. BUKALO[1], Y. TANISUMI[2,3], R. O'SULLIVAN[1], A. MENDEZ[1], S. ZIMMERMAN[1], V. OFFENBERG[1], O. CARPENTER[1], H. BHAGWAT[1], J. GOLDSCHLAGER[1], S. MOSLEY[1], L. R. HALLADAY[4], H. WAKE[5,3], A. HOLMES[1]; [1]Natl. Inst. of Health, Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD; [2]Lab. of Neural Information, Grad. Sch. of Brain Science, Doshisha Univers, Kawanishi-Shi / Hyogo, Japan; [3]Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sciences, Natl. Inst. of Natural Sci., Okazaki, Japan; [4]Santa Clara Univ., Santa Clara, CA; [5]Dept. of Anat. and Mol. Cell Biol., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan

Abstract: Biological systems designed to detect and respond to threats are critical for survival, activating defensive responses through associative learning. When a previously threatening stimulus becomes harmless, extinction learning occurs, creating a new inhibitory memory that coexists with the original fear memory. The basolateral amygdala (BLA) is a central hub in the brain that manages the balance between fear and extinction memories. Recent research suggests that the interplay between different groups of neurons, either anatomically or functionally distinct, helps regulate the shift between fear states. Although these studies have greatly enhanced our understanding of how fear memories are regulated at a neural circuit level, they have primarily focused on neurons. Here, we investigate the mechanisms through which astrocytes, the most abundant subgroup of glial cells, support the neural representation of fear memories and their extinction. First, by employing *in vivo* fiber photometry and two-photon Ca^{2+} recordings, we found that BLA astrocyte Ca^{2+} activity dynamically tracks shifts in fear state that are evident as mice retrieve, extinguish, and renew fear. Furthermore, by manipulating BLA astrocytes chemogenetically—using viral vectors to express hM3Dq- or hM4Di-coupled DREADDs — we demonstrated that administering clozapine N-oxide (CNO) bidirectionally altered fear retrieval and produced opposite effects on astrocyte Ca^{2+} activity. Finally, our results show that dynamic Ca^{2+} activity in astrocytes not only correlates with but also enhances the encoding of fear-related cues by BLA neurons, enriching the motivational relevance of the information in the neuronal population. This study reveals a critical role for astrocytes in memory retrieval and modifies existing neuron-centric models by incorporating the contributions of astrocytes in the amygdala's representation of fear states.

Disclosures: O. Bukalo: None. **Y. Tanisumi:** None. **R. O'Sullivan:** None. **A. Mendez:** None. **S. Zimmerman:** None. **V. Offenberg:** None. **O. Carpenter:** None. **H. Bhagwat:**

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Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.16/P12

Topic: G.04. Emotion

Title: Role of central amygdalar serotonergic and dopaminergic systems in the generation of anger-like responses in rats

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Abstract: Abstract Anger is a fundamental emotion characterized by feelings of hostility, frustration, or social provocation and agitation that play an integral role in affective life. Until now, researchers have made few attempts to uncover the neurobiology of anger, yet their understanding of its central mechanisms remains extremely limited. Earlier, studies suggested that the reduction of serotonin (5-hydroxytryptamine, 5-HT) and the elevation of dopamine (DA) in the central nucleus of the amygdala (CeA) are associated with anger and aggressive-like behaviour. In light of the above, we hypothesize that the interaction between 5-HT and DA, in the framework of CeA may be crucial for the processing of anger. To test the hypothesis, rats were kept on 48-hour food restriction (48-h FR) and the biting activity was monitored in the behavioural chamber, wherein the rats were allowed to see and smell the food, but access was denied. We pre-administered 5-HT/DA agonists and antagonists to the rats to evaluate the role of dopaminergic and serotonergic systems in modulating behaviour, and then evaluated the changes in their biting activity. Immediately after the behavioural task, the changes in the CeA were evaluated in terms of (1) immunohistochemical profile using antibodies against 5-HT1A, (2) expression of mRNA for the receptors of DA (D1 and D2) and 5-HT1A using RT-qPCR, and (3) release of 5-HT, 5-HIAA, DA and DOPAC by using HPLC-ECD method. The 48-h FR rats with denied food access significantly increased the number of bites and biting duration as compared to the fed group. Herein, we considered the number of bites and biting duration as indicators of an anger-like response. Intra-CeA treatment of D2 agonists (quinpirole, intra-CeA) or 5-HT1A antagonists (WAY100635, intra-CeA) potentiated the anger-like response, while treatment of D2 antagonists (sulpiride, intra-CeA) attenuated it. In addition, combination treatment of quinpirole and WAY100635 at subeffective doses significantly elevated the anger-like response in 48-h FR rats. Moreover, 5-HT1A receptor immunoreactivity has been significantly reduced, and D1 and D2 receptor mRNA gene expressions have increased dramatically in the CeA of anger-induced

rats. The microdialysis study revealed a significant increase in DA and DOPAC levels during the anger-like response. Thus, we conclude that central amygdalar serotonergic and dopaminergic systems are involved in the processing of anger-like responses in rats.

Disclosures: D.K. Sahare: None. **B.B. Dudhabhate:** None. **N.K. Subhedar:** None. **D.M. Kokare:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.17/Q1

Topic: G.01. Fear and Aversive Learning and Memory

Support: FAPESP 2021/04949-1
CAPES-PROEX 001
FAPESP 2022/02986-0

Title: Role of D2-Like Dopaminergic Receptors in the Inferior Colliculus on Unconditioned and Conditioned Fear Responses

Authors: *C. DE OLIVEIRA ALVES[1], A. R. DE OLIVEIRA[2];
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Abstract: Dopamine is one of the most active neuromodulators in mechanisms underlying states of fear and anxiety. Depending on the threatening condition (conditioned or unconditioned), blocking D2-like dopaminergic receptors can reduce or increase aversion, suggesting a dual role for dopamine in aversive states. The present study evaluates the effects of blocking D2-like dopaminergic receptors in the inferior colliculus (IC) on unconditioned and conditioned fear in male and female rats at different estrous cycle stages. The effects of intra-IC administration of sulpiride (D2-like antagonist; 0, 2, and 4 μg/0.2 μL) were evaluated on the elevated plus maze test (EPM) and contextual conditioned fear protocol in 111 adult Wistar rats (37 males and 74 females; CEUA protocol 8014150921). Female rats were divided into proestrus/estrus and metestrus/diestrus groups based on vaginal smear analysis. On day 1, after receiving sulpiride or vehicle in the IC, animals underwent the EPM test. Day 2 marked the start of the contextual conditioned fear protocol, involving a training session with footshock presentations. On day 3, sulpiride or vehicle was administered into the IC before the fear conditioning test session to assess freezing response, followed by a retest on day 4. Statistical analysis comprised one- and two-way ANOVAs, with Tukey's post hoc test for significance ($p < 0.05$). Intra-IC injections of sulpiride reduced EPM entries in the open arms ($F_{2,31} = 4.97$; $p < 0.05$), time spent in the open arms ($F_{2,31} = 4.11$; $p < 0.05$), and exploration of the open arms extremities ($F_{2,31} = 7.07$; $p < 0.05$) in metestrus/diestrus females, indicating an impact on unconditioned fear. Notably, no significant effects were observed in males or proestrus/estrus females ($p > 0.05$). Regarding conditioned

fear, intra-IC sulpiride reduced freezing behavior during test and retest sessions in males ($F_{2,34}$ = 19.30, $p < 0.05$), proestrus/estrus females ($F_{2,34} = 31.60$, $p < 0.05$), and metestrus/diestrus females ($F_{2,34} = 23.60$, $p < 0.05$). Based on the results, blocking D2-like dopaminergic receptors in the IC appears to have a sex- and estrous cycle-dependent pro-aversive effect on unconditioned fear, while showing a more generalized anti-aversive effect on conditioned fear.

Disclosures: C. de Oliveira Alves: 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.; FAPESP. **A.R. de Oliveira:** None.

Poster

PSTR480: Fear and Threat Representations

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR480.18/Q2

Topic: G.01. Fear and Aversive Learning and Memory

Support: K08 MH122733
United States Department of Defense
VA National Center for PTSD
T32 NS041228

Title: The Interplay of Stress Regulators: Corticotropin-Releasing Factor and Norepinephrine Interactions in Threat

Authors: *J. COOK[1], A. BASU[2], S. M. STASZKO[3], J.-H. YANG[1], Y. LI[4], A. P. KAYE[5]; [1]Psychiatry, Yale Univ., New Haven, CT; [2]Psychiatry, Yale Univ. Interdepartmental Neurosci. Program, New Haven, CT; [3]Anat. and Neurobio., Yale Univ., Branford, CT; [4]Peking Univ., Beijing, China; [5]Dept. of Psychiatry, Yale Univ., New Haven, CT

Abstract: Experiencing trauma can induce enduring changes in regions of the brain associated with stress response, such as the medial prefrontal cortex (mPFC), locus coeruleus, paraventricular hypothalamus (PVH), and bed nucleus of the stria terminalis (BNST). Dysregulation of corticotrophin-releasing factor (CRF), a neuropeptide, has been linked to trauma-related disorders, with genome-wide association studies implicating CRF receptor 1 (CRFR1) in posttraumatic stress disorder risk. To explore CRF's role in processing stress-related threats, we investigated its involvement in moment-to-moment threat processing sensitized by stress. Employing computational behavior tracking, pharmacological interventions, and neuropeptide sensor techniques within a stress-enhanced fear learning (SEFL) model of PTSD, our study revealed that administering a selective CRFR1 antagonist (antalarmin) mitigated stress-induced sensitization of contextual fear learning in SEFL. Moreover, computational behavior tracking (MoSeq) unveiled distinct stress-related behavioral states modulated by the CRFR1 antagonist. Using fiber photometry of genetically encoded neuropeptide sensors (GRAB-

CRF3.0), we observed CRF release in the mPFC in response to various threatening stimuli, including learned and innate fears. Subsequent GRAB-CRF3.0 recordings during the SEFL paradigm provided further insights into CRF dynamics during stress sensitization. Additionally, we will leverage two-photon imaging and optogenetic techniques to elucidate the specific functions of CRF release in learned versus innate threat processing. By elucidating neuropeptide dynamics underlying threat-related behaviors, our results offer implications for the potential therapeutic efficacy of CRFR1 antagonism in mitigating the effects of SEFL subsequent to traumatic stress exposure.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.01/Q3

Topic: G.08. Other Psychiatric Disorders

Support: McNair Foundation

Title: Single neuron encoding of audio-visual speech comprehension in human cortex

Authors: *M. FRANCH[1], A. WATROUS[2], E. BARTOLI[3], J. ADKINSON[2], S. A. SHETH[2], B. Y. HAYDEN[2];
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Abstract: Successful communication between individuals often relies on shared understanding of the meaning, or semantics, of spoken words and interpretations of visual social cues, such as body language and facial expressions. The idea of ‘the language network’ posits there are specific brain regions required for speech comprehension, such as left middle temporal gyrus and Wernicke’s area, based on evidence from lesion and neuroimaging studies. However, recent work suggests many brain regions outside of this traditional language network perform similar computations to support semantic processing. Along these lines, we hypothesize that activity in multiple brain regions covaries with the semantics of heard speech and that viewing social-emotional and speech cues from the speaker improves semantic encoding. To understand neural mechanisms of semantics from both visual and linguistic inputs, we are performing intracranial recordings from single neurons in human anterior cingulate cortex and hippocampus while participants listen to and watch different videos of speakers telling stories. We simultaneously record eye movements and the participant’s world view as they wear binocular eye tracking glasses, enabling us to capture moments when the patient is viewing the speaker or other objects in the room. By extracting semantic categories from word embeddings, we find that both ACC and HPC exhibit firing rate patterns that covary with semantic categories and can distinguish

social and non-social words. Preliminary results suggest that each brain region processes linguistic semantic information. Overall, this research uses naturalistic and imperative approaches such as organic storytelling, eye tracking, and single neuron electrophysiology to understand the neural basis of semantics, critical for identifying the neural circuitry of social cognition.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.02/Q4

Topic: G.08. Other Psychiatric Disorders

Title: Basal ganglia neurophysiological markers of depression in Parkinson's disease

Authors: *K. A. JOHNSON[1], P. B. COUTINHO[2], L. KENNEY[3], D. BOWERS[4], J. D. HILLIARD[5], K. D. FOOTE[5], G. PONTONE[2], C. DE HEMPTINNE[2];
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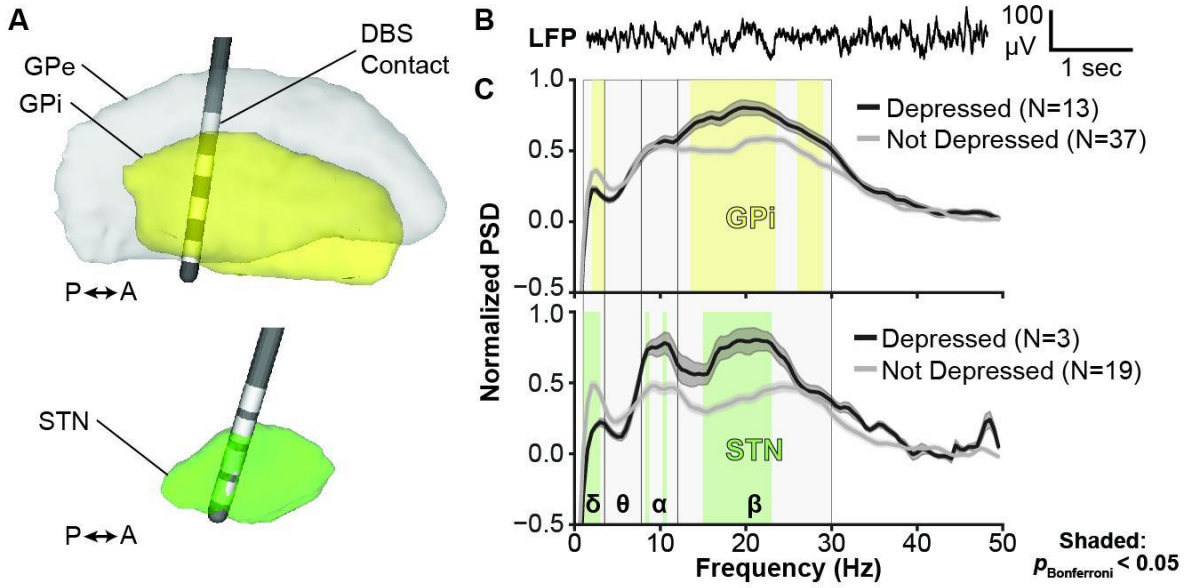
Abstract: Depression is a common debilitating nonmotor symptom of Parkinson’s disease (PD), but the underlying pathophysiology is not well understood. Previous studies have leveraged deep brain stimulation (DBS) to record basal ganglia neural activity associated with depression in PD. However, the results have been inconsistent and focused exclusively on the subthalamic nucleus (STN), leaving a gap in knowledge about the role of the globus pallidus internus (GPi). The goal of this study was to investigate neurophysiological markers of depression in PD in a large retrospective cohort undergoing GPi or STN DBS for PD.
In N=72 patients with PD (N=50 GPi, N=22 STN; N=50 male), we acquired 30 seconds of intraoperative local field potential recordings at 22 kHz sampling frequency from all monopolar contacts on the DBS lead while the patient was off-medication and at rest. The power spectral density was computed and normalized across patients. Preoperative off-medication Unified Parkinson’s Disease Rating Scale (UPDRS) and Beck Depression Inventory (BDI-II) scores were acquired to measure the baseline severity of motor symptoms and depression symptoms, respectively.
Patients with clinical depression symptoms (BDI-II >= 14) exhibited lower delta (1-4 Hz) power and higher beta (12-30 Hz) power in both the GPi and the STN, as well as higher alpha (8-12 Hz) power in the STN, compared to patients without depression symptoms (BDI-II < 14) (Fig 1; t-test at each frequency $p<0.05$, Bonferroni corrected). Beta power in the GPi was significantly correlated with depression symptom severity ($r=0.34$, $p=0.017$). However, baseline depression symptom severity, delta power, alpha power, and beta power were not significantly correlated with motor symptom severity ($p>0.05$).

Our results suggest that neural activity in the GPi may play a role in the pathophysiology of depression in PD independent of motor symptom severity. Future research will focus on localizing pathological signals and acquiring chronic recordings to understand the neural activity underlying depression in PD in the naturalistic environment.



Disclosures: K.A. Johnson: None. **P.B. Coutinho:** None. **L. Kenney:** None. **D. Bowers:** None. **J.D. Hilliard:** None. **K.D. Foote:** None. **G. Pontone:** None. **C. de Hemptinne:** 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.; Parkinson's Foundation.

Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.03/Q5

Topic: G.08. Other Psychiatric Disorders

Support: NICHD Grant 1P50HD103536

Title: An acute exercise intervention to ameliorate behavioral and neurophysiological indices of inhibitory control deficits in schizophrenia: a mobile brain/body imaging (MoBI) study

Authors: *V. A. POPOV[1], E. G. FREEDMAN[2], J. J. FOXE[3];
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Abstract: Background: Inhibitory control deficits are a core feature of schizophrenia spectrum disorders (SSDs), with clear manifestations seen in both psychophysiological and electrophysiological measures of these processes. Addressing these symptoms is of critical clinical relevance since they are a main predictor of negative vocational and psychosocial outcomes. An intriguing set of findings has suggested exercise can have a positive effect on SSD symptomatology, but the exercise-linked neural changes that may result in improved inhibitory control are unknown. **Methods:** Male and female individuals with SSDs (*n*= 16) and neurotypical, age-matched healthy controls (HCs) (*n*= 14) completed the Go/NoGo response inhibition (RI) task while sitting and walking. The emergence of Mobile Brain/Body Imaging (MoBI) technologies allowed for the successful assessment of cognitive control processes through high density electroencephalography (hd-EEG), behavioral performance on the RI task, and motoric function through motion capture technologies while participants were engaged in treadmill walking or were sitting. Here, we leveraged MoBI to ask whether a single acute exercise intervention, particularly treadmill walking in this study, would lead to improved performance on a canonical RI task, and if previously well-characterized deficits in the generation of inhibition-related event-related-potential (ERP) components can be ameliorated in individuals with SSDs. **Results:** Simple main effects analysis showed that groups had a statistically significant effect on d' scores ($F(1, 29) = 11.30$, $p = .001$) and motion state did not ($F(1, 29) = 0.20$, $p = .65$). The cluster-based permutation approach showed significant ERP amplitude increases during walking over frontal and frontocentral scalp regions and reductions over parietal and occipital scalp regions during RI related ERP component intervals for controls and SSDs, and earlier in controls. **Discussion:** Preliminary findings suggest a single intervention of treadmill walking showed no improvement in inhibitory control performance but normalization of neurophysiological processes in SSDs to those of controls. To our knowledge, this is the first study of its kind to date to examine inhibitory control in real time during an acute exercise intervention. A longer-term fitness intervention trial could assess whether these positive outcomes can be established more durably.

Disclosures: V.A. Popov: None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

PSTR481: Affect, Computation, Psychiatry

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Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant 1UH3NS115631
NIH Grant 1UH3NS109556

Title: Naturalistic decoding of chronic pain states towards adaptive brain stimulation

Authors: *P. SHIRVALKAR[1], J. SAAL[4], J. LIN[2], R. LERICHE[3], K. K. SELLERS[5], P. A. STARR[6], E. F. CHANG[7];

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Abstract: Chronic pain affects 1 in 4 adults and is often refractory to treatment. Deep brain stimulation (DBS) for pain has been studied for over 70 years, but an objective biomarker that can guide therapy is still lacking. Previous research was limited by focusing on experimental pain tasks in healthy individuals, constraining clinical application. We performed a study to identify real-world brain biomarkers of naturalistic chronic pain to personalize DBS and clarify mechanisms of action.Using chronic intracranial electrodes, we recorded ambulatory neural signals from the anterior cingulate (ACC) and orbitofrontal cortex (OFC) in four chronic pain patients. Patient-reported pain symptoms were concurrently logged multiple times daily over six months. We used machine learning models to predict spontaneous chronic pain severity from brain power signals. Model significance was computed using a shuffled surrogate training dataset with leave one out cross validation.We predicted intraindividual chronic pain severity from neural activity with high sensitivity (range 0.62-0.84). Regression models performed moderately well (highest $R2 = 0.7$, $p<0.001$) on predicting pain intensity and unpleasantness from ACC and OFC power signals. Classification models performed better, with AUC ranging 0.6 - 0.85 ($p<0.001$). Chronic pain decoding relied on sustained power changes from the OFC, with OFC delta being common across patients. ACC features appeared more important for acute pain task decoding. OFC activity is sufficient to track the severity of clinical pain states over months. Brain representations of chronic pain are distinct from those for acute, physical pain. These biomarkers are being incorporated into closed loop control algorithms for personalized DBS.Here we will also present data on multi brain region recordings with stereoEEG and multimodal characterization of spontaneous pain states using wearable metrics and patient drawings. We will further demonstrate algorithms for controlling closed loop brain stimulation based on mechanistic insights of chronic pain encoding.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

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Program #/Poster #: PSTR481.05/R1

Topic: G.08. Other Psychiatric Disorders

Support: NIH BRAIN Initiative Grant UH3NS103549
Baylor Research Advocates for Student Scientists (BRASS) Funding

Title: Identifying ethologically relevant neurobehavioral biomarkers of emotional state

Authors: *K. KABOTYANSKI[1], H. YI[5], R. HINGORANI[6], B. S. ROBINSON[7], H. P. COWLEY[9], M. S. FIFER[8], B. A. WESTER[9], J. ADKINSON[2], E. BARTOLI[3], A. WATROUS[2], A. ALLAWALA[10], G. BANKS[1], N. POURATIAN[11], S. J. MATHEW[4], W. K. GOODMAN[12], B. Y. HAYDEN[1], N. R. PROVENZA[2], S. A. SHETH[2], *K. KABOTYANSKI[2];
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Abstract: Major depressive disorder (MDD) is the leading cause of disability and death from suicide. Emotion dysregulation is the hallmark of depression, so developing tools for objective, quantitative characterization of the temporal, behavioral, and neural dynamics underlying emotional state is critical for properly diagnosing and treating these debilitating conditions. We analyzed continuous, synchronized audio, video, and neural recordings during daily social interactions in human neurosurgical patients implanted with both stereo-EEG and deep brain stimulation (DBS) electrodes as part of a clinical trial (NCT03437928) for treatment-resistant depression (TRD). We then developed a pipeline for automated transcription with diarization and utterance-level timestamps of audio recordings. Pre-trained affective computing models were then used for extraction of linguistic, acoustic, and kinesic features associated with emotional state. These behavioral features were then correlated to brain-wide features of concurrent neural activity. Finally, we used a multi-modal intermediate fusion model to investigate whether cross-modal features can better predict self-reported affect and neural activity, than a single modality alone. Both content-relevant (linguistic) and content-irrelevant (acoustic, kinesic) features were correlated with asynchronous self-reported affect, as well as with brain-wide neural features previously found to be associated with mood. Cross-modal behavioral features associated with positive emotional state also showed a positive correlation with high-gamma activity in limbic regions. Natural conversations provide a wealth of objective, quantifiable behavioral data that is highly temporally resolved and closely aligned with underlying neural activity. By relating linguistic features from “what” is expressed, as well as acoustic and kinesic features from “how” it is expressed, to simultaneous neural activity, we can build multi-modal models for more effective diagnosis, assessment, and treatment of affective disorders.

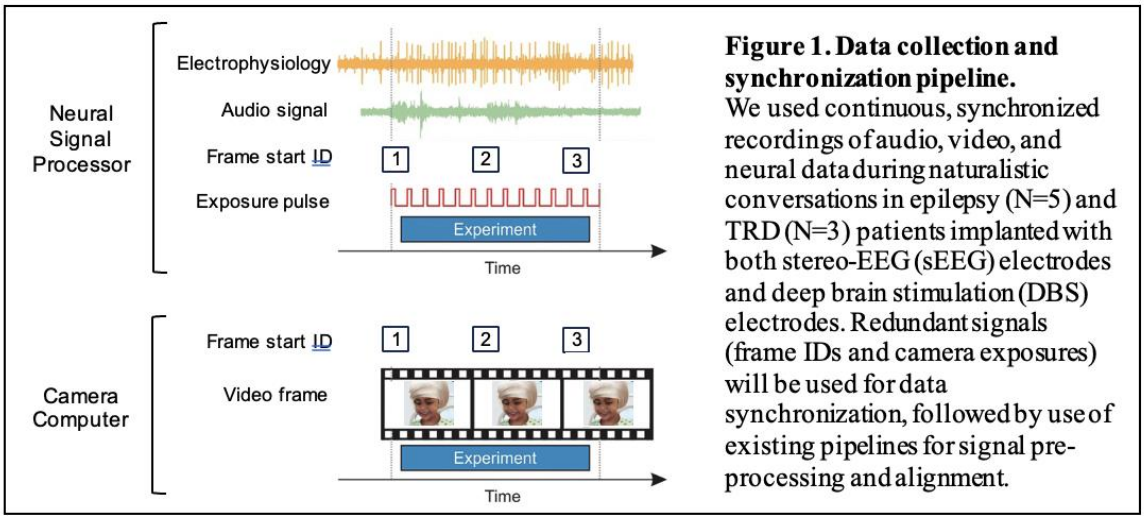

Figure 1. Data collection and synchronization pipeline. We used continuous, synchronized recordings of audio, video, and neural data during naturalistic conversations in epilepsy (N=5) and TRD (N=3) patients implanted with both stereo-EEG (sEEG) electrodes and deep brain stimulation (DBS) electrodes. Redundant signals (frame IDs and camera exposures) will be used for data synchronization, followed by use of existing pipelines for signal pre-processing and alignment.

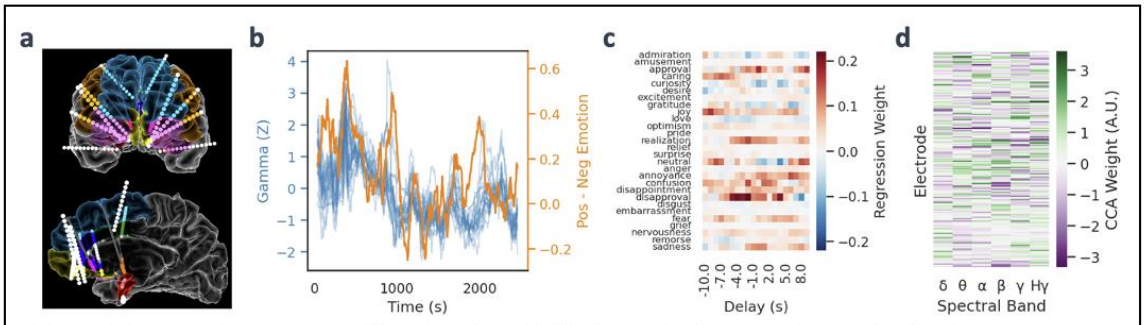

Figure 2. Neural analyses linking limbic activity to content-relevant emotion features. 3D reconstruction of sEEG leads implanted in a TRD patient (**b**) Brain-wide neural timeseries (blue) of Z-scored gamma band power overlaid with emotion timeseries (orange) based on extracted linguistic features. (**c**) Temporal response profiles for all emotion states in the gamma band in the left medial prefrontal lobe. (**d**) Spatio-spectral feature map of a canonical component that encodes positive versus negative emotions, based on linguistic features from text transcript analysis.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.06/R2

Topic: G.08. Other Psychiatric Disorders

Title: Neural encoding of the world-model during naturalistic tasks

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Abstract: Compromised cognitive control is a hallmark of many psychiatric diseases, including depression and anxiety disorder. Effective cognitive control can be deployed to respond to changing goals by overriding responses that would otherwise be performed automatically. To probe cognitive control in the laboratory, psychiatrists often use laboratory tasks, such as the Stroop and Flanker tasks. These tasks have proven invaluable in psychology, psychiatry, and neuroscience. However, they have limited ecological validity, which may reduce their probative value. That limitation can be circumvented using naturalistic tasks (Chericoni & Hayden, 2023). We have developed a novel prey-pursuit task wherein participants control a joystick to pursue fleeing virtual preys on a computer monitor. In this task cognitive control involves continuous monitoring, prediction, and adjustment. We examined the behavior of 8 human participants performing this task in the epilepsy monitoring unit. We were especially interested in how different hypothesized elements of canonical control systems were reified in neuroanatomy. In particular, we hypothesized that the world model would be reified in the hippocampus. In general, the world model is an internal neural representation of the external world; containing information on the past and current states of the world; it is essential for flexible on-line adjustments in behavior. We recorded single-neuron activity in the anterior cingulate cortex (ACC) and hippocampus of epilepsy patients performing the prey-pursuit task. We used a linear-nonlinear generalized model (LN-GLM) to fit world-centric, avatar-centric multi-agent variables tuning models to neuron responses. We found that neurons in both the ACC and in the hippocampus multiplex task-related variables with explicit representation of absolute variables (current position, speed and direction of the self and the prey) and relative variables (distance and angle between the self and the prey). Our results provide a demonstration that the human ACC and hippocampus can explicitly represent spatial and non-spatial variables highlighting their role in goal-oriented cognition.

Disclosures: A. Chericoni: None. **J.M. Fine:** None. **E. Bartoli:** None. **A. Watrous:** None. **J. Adkinson:** None. **S.A. Sheth:** None. **B.Y. Hayden:** None.

Poster

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Program #/Poster #: PSTR481.07/R3

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant UH3NS100549
NIH Grant UH3NS103549
NIH Grant R01MH130597
NIH Grant U01NS121472

Title: Enabling chronic neuromodulation research with a robust distributed data framework

Authors: *T. M. FRACZEK[1], P. J. STEFFAN[1], R. A. BECHTOLD[2], Y. ZHOU[1], J. ADKINSON[3], K. KABOTYANSKI[3], E. BARTOLI[4], B. Y. HAYDEN[5], A. WATROUS[3], N. VANEGAS[1], W. K. GOODMAN[6], S. A. SHETH[3], J. A. HERRON[7], N. R. PROVENZA[3]; [1]Baylor Col. of Med., Houston, TX; [2]Bioengineering, Univ. of Washington, Seattle, WA; [3]Neurosurg., Baylor Col. of Med., Houston, TX; [4]Dept. of Neurosurg., Baylor Col. of Med., Houston, TX; [5]Duke Univ., Durham, NC; [6]Psychiatry, NIMH, Bethesda, MD; [7]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: Recent neuroscience research increasingly relies on collecting chronic distributed data from implantable, wearable, and deployed devices, allowing numerous insights on how to individualize treatments and generalize them to the patient's home environment. For example, next-generation adaptive deep brain stimulation (aDBS) studies for Parkinson's, treatment-resistant bipolar depression, and obsessive-compulsive disorder involve constant collection of concurrent neural, video, and wearable sensor data. This comprehensive chronic monitoring approach, therefore, generates an immense amount of data that must be managed with great care. Any data that is lost, corrupt or incomplete requires prohibitive amounts of time or money to recover. In many cases, the experiments cannot be repeated. This means that each research team must develop a custom data management solution, leading to a large overhead before data collection can begin. We present a framework that is designed to enable fully automated data collection, improve data management, and facilitate data sharing. The framework is composed of several interacting packages, "Source", "Central", and "Client", each of which assists with a different part of the data management pipeline. The "Source" package is designed to move the data from its original collection point to a central storage location in a robust and repeatable manner, while helping the research team comply with data security standards. It also performs extensive automatic metadata collection at each step of the process, including version control information of the code itself. The metadata allows the "Central" package to understand the data so it can be automatically parsed into an hdf5 store and indexed. Researchers in the lab can then use the "Client" package to search for data and efficiently ingest it into their own analysis pipelines using existing tools. The data can also be exported into the NWB format, so that it can be easily shared with collaborators. The framework has already successfully been deployed as a part of several independent research projects. It allows the research teams to deploy our research system significantly faster and ensures a higher quality of data collected. The automation aspects of the pipeline allow researchers to collect multi-modal data 24/7. The structured and searchable nature of the data storage accelerates analysis and leads to more reproducible results.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.08/R4

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant R01MH124761
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Title: Amygdala Reactivity in PTSD and Anxiety Through Naturalistic Behavioral Tasks

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Abstract: We previously reported amygdala theta power elevations during aversive stimulus processing, retrieval of traumatic memories and the experience of heightened subjective fear and reexperiencing in individuals with treatment-resistant PTSD (TR-PTSD) (Gill & Schneiders et al 2023). Findings bridge decades of rodent research to human disease; however, the relationship between amygdala activity and real-time fear memory formation in humans and its variation along a continuum of anxiety severity remain uncharacterized. In this study, we investigate human behavioral and intracranial electroencephalography (iEEG) findings obtained from behavioral tasks conducted in both stationary and ambulatory settings, involving participants with and without TR-PTSD and with varying anxiety levels as measured by the State Trait Anxiety Inventory (STAI). Amygdala iEEG recordings were obtained during exposure to aversive images, trauma reminders, at-home symptoms, and fear conditioning tasks (a stationary computerized shape task [C-FCT] vs. ambulatory and stationary versions of an immersive virtual reality task [VR-FCT]). Our results reveal an augmentation in amygdala theta power during exposure to aversive stimuli, independent of sensory modality (aversive images vs. audio in C-FCT vs. audio, visual, stationary, ambulatory in VR-FCT). Furthermore, behavioral paradigms evoked skin conductance response (SCR) reactivity to aversive stimuli, which exhibited correlations with STAI scores. Additionally, heightened amygdala theta activity was observed during conditioned stimuli predictive of an aversive outcome (CS+) compared to non-predictive stimuli (CS-), with this effect being associated with participants' memory of stimulus-outcome

contingencies and SCR reactivity during the VR-FCT. In conclusion, our study juxtaposes amygdala reactivity across fear memory tasks conducted in diverse laboratory-based and naturalistic environments, encompassing individuals with varying levels of anxiety. These findings contribute to bridging the gap between experimental settings and real-life experiences, employing naturalistic tasks to elucidate the connection between clinical symptoms and human intracranial neurophysiology.

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Poster

PSTR481: Affect, Computation, Psychiatry

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Program #/Poster #: PSTR481.09/R5

Topic: G.08. Other Psychiatric Disorders

Support: NIH UH3 NS103549
JHU/APL Project Catalyst Grant

Title: Cross-modal integration methods to elucidate behavioral manifolds for neurobehavioral analysis

Authors: *R. HINGORANI[1], H. G. YI[1], K. KABOTYANSKI[2], B. S. ROBINSON[1], H. P. COWLEY[1], M. S. FIFER[1], B. A. WESTER[1], G. P. BANKS[2], S. J. MATHEW[3], W. K. GOODMAN[3], B. Y. HAYDEN[2], N. R. PROVENZA[2], S. A. SHETH[2];
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Abstract: Accurate characterization of behavior is crucial for developing a mechanistic understanding of neurobehavioral disorders. To this end, there is emerging interest in using high-fidelity multimodal data streams, such as video and audio recordings, to objectively quantify complex manifestations of human behavior. Integrating information across these disparate modalities, however, poses a significant analytical challenge due to the inherent heterogeneity across these data streams (e.g., data format, time resolution, etc.). As such, a well-established computational method for cross-modal integration is currently lacking in neurobehavioral research. Recent advances in artificial intelligence (AI) have shown great promise in extracting latent features from individual modalities using raw input data (e.g., wav2vec 2.0 model for extracting speech audio features) and aggregating information across these modalities. In this study, we explored emerging cross-modal machine learning approaches to capture behavioral

manifolds of interest and find their neural correlates. We analyzed a single patient's data as part of an ongoing clinical trial for deep brain stimulation (DBS) for treatment-resistant depression (TRD), which includes high-resolution stereoelectroencephalography (SEEG) data collected from the frontolimbic regions and dense, multimodal behavior data from facial video, speech audio, and text transcript during natural conversations designed to elicit different affective states. We showcase novel cross-modal approaches that range in the level of fusion from modality-agnostic aggregation of raw features at the earliest stage of deep network models to having the model first extract modality-specific latent features and aggregate at an intermediate network layer. Our results highlight the utility of these cross-modal approaches in accounting for variance in the intracranial neural data driven by complex behavioral dynamics. The analytical insights from this work have the potential to accelerate scientific discovery in a number of domains by unveiling new brain-behavior relationships. Future research will test the generalizability of the findings to other behavioral modalities as well as the robustness of the approach in more naturalistic environments.

Disclosures: R. Hingorani: None. **H.G. Yi:** None. **K. Kabotyanski:** None. **B.S. Robinson:** None. **H.P. Cowley:** None. **M.S. Fifer:** None. **B.A. Wester:** None. **G.P. Banks:** None. **S.J. Mathew:** None. **W.K. Goodman:** None. **B.Y. Hayden:** None. **N.R. Provenza:** None. **S.A. Sheth:** None.

Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.10/R6

Topic: G.08. Other Psychiatric Disorders

Support: 1UH3NS123310-01A1

Title: Multiscale Decoding of Chronic Mood Fluctuations in Human Treatment-Resistant Depression

Authors: *P. NANDINI[1,2,3,4], K. K. SELLERS[5,4], J. FAN[6,4], D. ASTUDILLO[7,4], A. ALLAWALA[5,4], V. R. RAO[6,4], L. P. SUGRUE[8,4], K. W. SCANGOS[7,4], A. KRYSTAL[7,4], E. F. CHANG[5,4], A. KHAMBHATI[5,4];
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Abstract: *Rationale:* Mood disorders are characterized by seemingly random fluctuations in mood and behavior. The ability to decode and forecast a patient's mood would enable clinical preparedness and preventative strategies to preemptively combat states of distress. Crucial unresolved questions include whether mood symptoms show coordinated fluctuations over time and how these fluctuations are encoded by brain activity in mood networks. Prior work shows multidien rhythms in brain activity can predict epileptic seizures (Baud et al., 2018). Here we use chronic intracranial recordings from treatment-resistant depression (TRD) patients to investigate the hypothesis that different dynamotypes (timescale rhythms) - trends and multidien rhythms - exist in both neural physiology and mood in TRD.
Methods: Three TRD patients in the PRESIDIO clinical trial (NCT04004169) were implanted with the NeuroPace, Inc. Responsive Neurostimulation System, with electrodes placed in the orbitofrontal cortex, amygdala, subgenual cingulate, and ventral capsule/ventral striatum (location independently determined for each patient (Scangos et al., 2021a, 2021b). Scheduled & participant-triggered intracranial EEG (iEEG) recordings were obtained multiple times a day over 2-4 years, along with self-reported mood scores through the Visual Analog Scales (VAS) of depression, anxiety & energy administered digitally through REDCap (Harris et al., 2019, 2009). Analysis involved an unsupervised clustering to identify spectro-spatial clusters reflecting temporally correlated patterns of brain activity, non-linear regression for trends, modularity analysis and Morlet wavelet convolution for multidien rhythms, and coherence to assess synchrony between neural & mood rhythms.
Results: Different dynamotypes were observed in iEEG signals and mood symptoms across all patients. Long-term trends were found in iEEG (R^2: 0.5-0.62, $p<0.0001$) and mood (R^2: 0.03-0.52, $p<0.05$). Multidien rhythms with 15-35 & 74-104 day periods ($p<0.001$) were found in both iEEG and mood. Spectral coherence between neural and mood rhythms ranged from 0.33-0.68, indicating synchronous fluctuations.
Conclusions: We present novel evidence of long-term trends and multidien rhythms in mood and neurophysiology in depression, showing significant coherence between these rhythms. This deepens our understanding of neural representation of multiple timescales of mood variability and could lead to novel biomarkers for both acute and chronic phases of depression. Crucially, predicting these rhythms could profoundly impact clinical strategies, improving preparedness and interventions in psychiatric care.

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Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

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Program #/Poster #: PSTR481.11/S1

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant UH3NS123310-01A1
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Title: Modulation of network dynamics associated with symptom state in treatment-resistant depression

Authors: *A. ALLAWALA[1], A. KHAMBHATI[1], K. K. SELLERS[2], D. ASTUDILLO[1], N. STAPPER[1], A. G. TREMBLAY-MCGAW[1], I. CHOI[1], L. P. SUGRUE[1], K. SCANGOS[3], E. F. CHANG[4], A. D. KRYSTAL[1];
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Abstract: Adaptive and closed-loop deep brain stimulation (DBS) therapy for psychiatric disorders have shown increasing promise in alleviating symptoms over the past decade. Recent efforts implementing closed-loop DBS have employed intracranial EEG-derived, individualized biomarkers of symptom severity (measured by self-reported surveys) to trigger DBS. However, the response of such biomarkers to DBS is inadequately understood, and self-report surveys to measure symptom severity are sparsely sampled and insufficient in capturing naturalistic behavior. The objectives of this study are to 1) identify differences in individualized vs. group-level neural biomarkers 2) evaluate the response of neural biomarkers of symptom severity following therapeutic DBS for treatment-resistant depression (TRD) and 3) leverage speech recordings from patients as a naturalistic behavioral measure of symptom state. In our study, five subjects with TRD were implanted with stereo-EEG electrodes, with distal contacts targeting the orbitofrontal cortex(OFC), amygdala, hippocampus, the bed nucleus strias terminalis(BNST), ventral capsule/ventral striatum(VC/VS) and the subcallosal cingulate(SCC). Ambulatory intracranial recordings were collected across 10 days, during which self-reported symptoms and clinician ratings were collected multiple times a day, interspersed with unilateral acute stimulation in the lateral OFC, SCC and the BNST/VC respectively. In two patients, we additionally collected continuous audio during clinician interviews and unstructured conversations. We analyzed power density spectra across these high-density recordings on a subject-level and group-level basis. We found distinct spectral power bands highly correlated with symptom severity in individual subjects. Sites with significant correlations among the subjects included: amygdala (Subjects 1 and 4; $p < 0.05$), hippocampus (Subject 1 and 4; $p = <0.05$), OFC and SCC (Subject 2;$p < 0.01$) and BNST/VC (Subject 5; $p < 0.01$). However, group-level biomarker analyses did not elicit any significant site-specific biomarkers highly correlated with symptom severity. In two subjects, stimulation in the BNST/VC significantly improved mood, decreased subject-specific biomarker spectral power in the Amygdala and VC. In one subject, BNST/VC stimulation increased speech rate, volume, and positive affective content in speech. Our findings indicate the importance of identifying biomarkers of clinical symptom severity at the personal level, and the need for future work on the effect of DBS on biomarkers, as well as incorporating naturalistic behavior to understand symptom states.

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Poster

PSTR481: Affect, Computation, Psychiatry

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.12/S2

Topic: G.08. Other Psychiatric Disorders

Support: NIH UH3NS100549

Title: Disruption of neural periodicity predicts clinical response after deep brain stimulation for obsessive-compulsive disorder

Authors: *N. R. PROVENZA[1,5], S. D. REDDY[1,2], A. K. ALLAM[1], S. V. RAJESH[1], N. DIAB[1], G. REYES[1], R. M. CASTON[6], K. A. KATLOWITZ[1], A. D. GANDHI[1], R. A. BECHTOLD[9], H. Q. DANG[1], N. GIRIDHARAN[1], K. E. KABOTYANSKI[1], F. MOMIN[1], M. HASEN[1], G. P. BANKS[1], B. J. MICKEY[7,8], B. SHOFTY[6], B. Y. HAYDEN[1,5,3], J. A. HERRON[10], E. A. STORCH[4], A. B. PATEL[5,3], W. K. GOODMAN[1,5,4], S. A. SHETH[1,5,3,4];
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Abstract: Recent advances in surgical neuromodulation have enabled chronic and continuous intracranial monitoring during everyday life. We used this opportunity to identify neural predictors of clinical state in twelve individuals with treatment-resistant obsessive-compulsive disorder (OCD) receiving deep brain stimulation (DBS) therapy (NCT05915741). All patients received a DBS generator that can record spectral power within a 5 Hz wide band at a selected center frequency. In the first few participants, we noticed a narrow-band peak in ventral striatum spectral power at the theta-alpha border (at or near 9 Hz). Given the prominence of this neural feature and its role in cognitive neurophysiology, we chose 9 Hz as the center frequency to track upon implantation of the DBS system. We thus obtained chronic, passive recordings in this band at continuous 10-minute intervals in all participants (316 ± 128 days total duration per patient; 25 ± 20 days before VS DBS activation and 292 ± 136 days after). We developed our neurobehavioral models based on these continuous neural recordings in an initial cohort of five patients and tested and validated them in a held-out cohort of seven additional patients. Prior to DBS activation, in the most symptomatic state, theta/alpha (9 Hz) power evidenced a prominent

circadian pattern and high degree of predictability. In patients with persistent symptoms (non-responders), predictability of the neural data remained consistently high. On the other hand, in patients who improved symptomatically (responders), predictability of the neural data was significantly diminished. In order to capture this feature, we fit a linear autoregressive model to the time series of 9 Hz power and computed a daily goodness of fit (R^2) between the true and predicted data. The daily R^2 values corresponding to the severe symptom state were significantly greater than those of the symptom unburdened state ($p<10^{-15}$). We then trained a classifier using these daily predictability measures using a leave-one-patient-out cross validation strategy and achieved accurate classification of clinical status with a balanced accuracy of 82%. Classifier performance was well above chance level ($p\approx0$). This neural feature accurately classified clinical status even in patients with limited duration recordings, indicating generalizability that could facilitate therapeutic decision making.

Disclosures: N.R. Provenza: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH National Institute of Neurological Disorders and Stroke BRAIN Initiative. **S.D. Reddy:** None. **A.K. Allam:** None. **S.V. Rajesh:** None. **N. Diab:** None. **G. Reyes:** None. **R.M. Caston:** None. **K.A. Katlowitz:** None. **A.D. Gandhi:** None. **R.A. Bechtold:** None. **H.Q. Dang:** None. **N. Giridharan:** None. **K.E. Kabotyanski:** None. **F. Momin:** None. **M. Hasen:** None. **G.P. Banks:** None. **B.J. Mickey:** None. **B. Shofty:** None. **B.Y. Hayden:** None. **J.A. Herron:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH National Institute of Neurological Disorders and Stroke BRAIN Initiative. **E.A. Storch:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH National Institute of Neurological Disorders and Stroke BRAIN Initiative. **A.B. Patel:** None. **W.K. Goodman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH National Institute of Neurological Disorders and Stroke BRAIN Initiative. **S.A. Sheth:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH National Institute of Neurological Disorders and Stroke BRAIN Initiative.

Poster

PSTR481: Affect, Computation, Psychiatry

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR481.13/S3

Topic: H.03. Decision Making

Support: NIH Grant RF1DA055666
NIH Grant U19NS107613

Title: Functional cell types and the linear dimension of neural manifolds

Authors: *C. LANGDON, T. A. ENGEL;
Princeton Univ., Princeton, NJ

Abstract: Single cortical neurons show complex responses during cognitive tasks, and dimensionality reduction has been a successful approach for finding structure in this heterogeneous neural activity. When applied to neural response patterns in a population state space, in which each axis represents activity of one neuron, dimensionality reduction methods often reveal low-dimensional neural manifolds encoding behaviorally relevant variables. Alternatively, we can view the same responses in a selectivity space, in which each axis represents a response feature (e.g., task condition) and each point is a neuron, to reveal the distribution of tuning properties across the population. Traditionally, these two views on neural activity were linked through the dynamics of neural circuits, with recurrently connected subpopulations, or functional types, generating low-dimensional response manifolds. However, recordings in prefrontal cortex indicate that although population activity lies on a low-dimensional manifold, individual neurons respond to seemingly random mixtures of task variables so that boundaries defining functional types are not apparent. Yet, recent experimental evidence of functional types in orbitofrontal cortex makes it unclear when functional types emerge in neural circuits and when neural computation can be understood in terms of the responses of single cells. Using a firing rate network model, we prove that functional types emerge in neural circuits exactly when neural manifolds are constrained to lie in low-dimensional linear subspaces. Moreover, we find that the number of functional types is approximately equal to the linear dimension of the underlying neural manifold, with equality arising in the limit of strict low-dimensionality. We confirm these predictions in both task-optimized recurrent neural networks and brain-wide neural recordings from mice during complex behavior. These findings explain the emergence of functional types in neural circuits and characterize the settings in which neural computation can be understood in terms of single cell responses.

Disclosures: C. Langdon: None. **T.A. Engel:** None.

Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.01/Web Only

Topic: H.03. Decision Making

Support: UNAM Grant IN214223
CONAHCyT Grant CF-2023I-225
CONAHCyT Grant 1047792

Title: Diazepam's Sex-Dependent Modulation of Risk-Reward Decision-Making

Authors: *O. ENCISO PABLO, F. SIERRA RAMIREZ, K. CRUZ PALOMEQUE, F. SOTRES-BAYON;
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Abstract: Diazepam, a benzodiazepine with anxiolytic properties, has been proposed to influence risk-reward decision-making. Prior work using a naturalistic foraging task demonstrated that a low dose of diazepam (1mg/kg) increased risk-taking behavior in rats facing conflict (Illescas-Huerta et al., 2021). Here, we examined the sex-specific influence of this low-dose diazepam administration on risk-reward decision-making in rats. We designed a platform-mediated avoidance paradigm with adjustable conflict levels, allowing the same animals to make choices under both low- (escape from shock with minimal risk by moving to a safe platform) and high-conflict (reward availability contingent upon a period associated with shock) conditions. We found that diazepam did not significantly affect behavior in either sex under low-conflict conditions. However, under high-conflict conditions, males exhibited greater risk-taking behavior compared to females. Interestingly, diazepam administration in this high-risk scenario reduced avoidance behavior and increased food-seeking in both sexes, suggesting a shift towards increased risk-taking. Notably, diazepam also reduced the sex difference in behavioral responses, leading to a convergence in risk-taking tendencies under its influence. These findings demonstrate the context-dependent influence of diazepam on risk-reward decisions and unveil sex-specific effects in rats. Further research is warranted to elucidate the underlying neurobiological mechanisms and broader implications for understanding the complex effects of diazepam on conflict-driven choice behavior.

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Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.02/S4

Topic: H.03. Decision Making

Support: NIH grant R21DA058160

Title: The Effects of Cannabinoid Receptor Manipulation on Punishment-driven Risky Decision-Making

Authors: *S. LOWE[1], T. G. FREELS[2], A. LILEY[3], D. B. GABRIEL[6], Z. MIKKELSON[4], J. LEONIDES MARTINEZ[7], H. J. SABLE[5], N. W. SIMON[3];
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Abstract: Risky decision-making is a hallmark of multiple psychological disorders, including substance use disorder and schizophrenia. Disorders characterized by aberrant decision-making are often associated with abnormalities in cannabinoid signaling. However, the precise impact of manipulating cannabinoid receptors on punishment-driven risky decision-making remains poorly understood. To address this, we tested the acute systemic effects of multiple cannabinoid drugs on punishment based risky decision-making in Long Evans rats. We measured risky behavior with the Risky Decision-Making Task (RDT), wherein rodents choose between a small safe reward (one food pellet) and a large reward (three food pellets) with a risk of mild shock that increases across five blocks of trials (0%, 25%, 50%, 75%, 100%). After rats achieved stability in RDT, we tested multiple doses of different cannabinoid drugs: THC, the primary psychoactive compound in cannabis plants which activates CB1 and CB2 receptors; ACEA, a selective CB1 receptor agonist; rimonabant, a CB1 receptor inverse agonist, and AA-5-HT, a fatty acid amide hydrolase inhibitor that prevents the breakdown of endocannabinoids, leading to enhanced endocannabinoid levels in the synapse. We observed that ACEA, Rimonabant, and AA-5-HT had no discernible effects on risky decision-making, decision latency, or omissions. In contrast, THC exhibited sex-dependent effects on risky decision-making. Female rats were unaffected by THC, but males demonstrated inflexible decision-making, measured as reduced slope across multiple doses. Collectively, these data suggest that risky decision-making is susceptible to systemic activation of the cannabinoid system by THC, but is unaffected by manipulation localized to the CB1 receptor. Furthermore, males are more vulnerable to cognitive effects of THC than females. Understanding how the cannabinoid system regulates risky decision-making is critical for development of treatments to improve decision-making in psychiatric disorders as well as cannabinoid misuse.

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Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.03/S5

Topic: H.03. Decision Making

Support: NIH grant R21DA058160

Title: The Effects of Repeated Exposure to Atypical Antipsychotics on Risky Decision-Making

Authors: *J. LEONIDES MARTINEZ[1], Z. MIKKELSON[1], A. CRICHTON[1], J. SIMMONS[1], R. BRINK[1], K. CORTES[2], Y. PASTOR-MORENO[1], S. LOWE[1], N. W. SIMON[3];
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Abstract: Atypical antipsychotics are used to treat several disorders associated with psychosis or mania, including schizophrenia and bipolar disorders. Aberrant risky decision-making is a common symptom of these disorders; however, little is known about how repeated exposure to antipsychotics affects risk-taking. We tested the impact of a chronic, escalating dose regimen of the atypical antipsychotic risperidone on risky decision-making in male and female adult Long Evans rats. Risk-taking was measured with the Risky Decision-making Task (RDT), which presents rats with a choice between a single sugar pellet and three pellets accompanied by increasing risk of mild footshock. With lower doses of risperidone (.1mg/kg), there was no significant effect of drug. However, when the dose was elevated to .2 mg/kg, this caused a significant drop in risky decision-making. Notably, female rats showed a greater increase in risk aversion than males. These data suggest that higher dose atypical antipsychotics cause sex-specific effects on punishment-driven risky decision-making. Follow-up experiments are in progress measuring the influence of two mechanistically distinct psychotomimetic drugs (DOI and MK-801) on RDT, followed by co-administered risperidone and psychotomimetics.

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Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.04/S6

Topic: H.03. Decision Making

Support: NIH Grant R21DA058160-01

Title: Lateral orbitofrontal cortex to ventral pallidum circuitry regulates decision-making with delayed punishment

Authors: *Z. N. MIKKELSON[1], G. L. MINNES[2], S. LOWE[1], N. PATTERSON[1], N. W. SIMON[1];
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Abstract: Cost/benefit decision-making requires assessment of all possible positive and negative outcomes to maximize reward and minimize punishment. However, punishments occurring later in time are often underestimated, potentially leading to maladaptive decision-making. Sensitivity to delayed punishment can be measured using the Delayed Punishment Decision-making Task (DPDT) in which rats choose between small, safe rewards and large rewards accompanied by

mild footshock. Critically, this shock is initially delivered immediately after choice, then preceded by an incrementally increasing delay. This reveals that, as in humans, rats "discount" the negative value of delayed punishment. Previous work has demonstrated that sensitivity to delayed punishment is regulated by the lateral orbitofrontal cortex (LOFC). However, it remains unclear which specific LOFC circuits are involved in sensitivity to delayed punishment during decision-making. Here, we investigated the roles of LOFC-ventral pallidum (VP) and LOFC-dorsomedial striatum (DMS) in decision-making in DPDT. We observed that VP inactivation via a baclofen/muscimol solution caused reduced choice of the large reward regardless of punishment delay. We then determined that chemogenetic suppression of the LOFC-VP circuit via inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) reduced the ability to adapt to changes in delay, possibly due to impaired ability to update outcome expectancies throughout the task. Currently, we are investigating the LOFC-DMS circuit via region-specific inactivation and chemogenetic circuit manipulation. Our data suggest that LOFC - VP communication is integral to decision-making with delayed punishment, with LOFC processing information about delays and VP regulating sensitivity to punishment. Our long-term goal is to lay a foundation for novel circuit-level treatments to improve aberrant decision-making in neuropsychological disorders.

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Poster

PSTR482: Decision-Making

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.05/T1

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Mesocortical and mesolimbic dopamine signaling in aversion, reward and decision making

Authors: *J. D. SCHUMACHER[1], M. LYSENKO-MARTIN[2], M. ZHAO[3], C. A. WINSTANLEY[1], S. B. FLORESCO[1];
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Abstract: Optimal risk/reward decision making is integral to human mental and physical health and relies on dopaminergic (DA) signalling. Risk/reward decision making is often studied using operant tasks such a probabilistic discounting which requires rats to choose between a small, certain and a large, risky reward whose probability varies systematically across blocks of trials. Prior work has shown that nucleus accumbens (NAc) DA, via D1 receptors, promotes preference for the large/risky reward whereas DA in the medial prefrontal cortex (mPFC) refines choice via

opposing action on D1 and D2 receptors. Microdialysis studies demonstrate that DA efflux in the NAc and mPFC tracked reward uncertainty and overall reward rates, respectively. However, DA release manifests as discrete phasic events and pharmacology and microdialysis lack the temporal resolution to disentangle these temporally specific effects. Preliminary data using optogenetic silencing of dopaminergic VTA neurons has demonstrated that silencing during receipt of either the large/risky or small/certain reward biases choice towards the other option. These changes in choice behavior are associated with changes to the propensity to follow an unrewarded large/risky choice with a small/certain choice (lose-shift behavior). Specifically, inhibition on large/risky and small/certain rewards increased and decreased lose-shift behavior, respectively. Parallel fiber photometry studies using fluorescent DA indicators (GRABDA3) have begun to investigate mPFC and NAc DA signalling in appetitive and aversive associative learning tasks. Specifically, we paired sugar reward delivery with a visual stimuli and then subsequently subjected rats to auditory fear conditioning. In the NAc, the amplitude of DA responses to appetitive CS and US presentation was higher than to aversive CS and US presentation. The opposite pattern was observed in mPFC with larger amplitudes of DA release in response to aversive CS and US presentation than appetitive US presentation and non-detectable DA release to appetitive CS presentation. Finally, in separate animals required to make forced choice nosepokes in 4 ports to obtain different magnitude rewards we observed larger rewards (3-4 pellets) elicited protracted, multiphasic NAc DA transients and smaller rewards (1-2 pellets) elicited similar amplitude but shorter DA events. Follow-up studies will expand these results to risk/reward decision making, examining how mPFC and NAC DA encode reward magnitudes and probabilities of different outcomes. Together, these findings will expand our understanding of DA signalling in complex decision-making behavior.

Disclosures: J.D. Schumacher: None. **M. Lysenko-Martin:** None. **M. Zhao:** None. **C.A. Winstanley:** None. **S.B. Floresco:** None.

Poster

PSTR482: Decision-Making

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Program #/Poster #: PSTR482.06/T2

Topic: H.03. Decision Making

Support: CIHR grant (PJT-186219)

Title: Differential Modulation of Cost/Benefit Decision Making and Motivation by Prefrontal Cortical CRF1 and 2 Receptors

Authors: *G. L. DALTON, S. MIRZAEI, **S. B. FLORESCO**;
Psychology and Ctr. for Brain Hlth., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Acute stress activates numerous systems in a coordinated effort to promote homeostasis, and can exert differential effects on mnemonic and cognitive functions depending

on a myriad of factors. Stress can alter different forms of cost/benefit decision-making, particular those involving physical costs such as punishment or effort. Previous work by our group has shown that stress reduces preference for larger vs smaller rewards associated with a greater effort cost and alters other measures of motivation. These effects are mediated in part by increased corticotropin-releasing factor (CRF). However, the specific brain regions and receptor mechanisms through which increased CRF activity may perturb these functions remained to be clarified. This study examined how increased activation of CRF 1 and 2 receptors in the medial prefrontal cortex (mPFC) may contribute to stress-induced alterations in cost/benefit decision-making, assessed using an effort discounting task. Male and female rats were well-trained to choose between a low effort/low reward lever (2 pellets) and a high effort/high reward lever (HR; four pellets), with the effort requirement increasing over a session (1, 5, 10, 20 presses). Intra-mPFC infusion of the CRF1 agonist stressin (0.1-0.2 ug) did not affect effort-related choice or decision latencies, and actually enhanced response vigor (rates of responding on the HR lever) in both sexes. In stark contrast, stimulation of mPFC CRF2 receptors with Urocortin3 (0.1-0.5 ug) reduced HR choice in the latter, higher effort blocks in males, and in the earlier blocks in females, that chose the HR option less often than male in the higher effort blocks. These treatments also increased response latencies in the highest effort block, without affecting response vigor. These data highlight how CRF1 and 2 receptor activity in the mPFC exerts opposing influences on cost/benefit decisions and reward-related motivation. CRF1 receptors enhance response vigor, whereas excessive activation of CRF2 receptors reduce preference to pursue larger rewards associated with a greater effort cost. This latter effect suggests that increased mPFC CRF2 activity may contribute to motivational impairments and perturbed decision-making associated with stress-related psychiatric disorders such as depression.

Disclosures: G.L. Dalton: None. **S. Mirzaei:** None. **S.B. Floresco:** None.

Poster

PSTR482: Decision-Making

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Program #/Poster #: PSTR482.07/T3

Topic: H.03. Decision Making

Support: CIHR grant (PJT-186219)

Title: Chemogenetic Stimulation of BNST Corticotropin-Releasing Factor Neurons Perturbs Effort-Related Choice

Authors: *M. ZHAO, J. D. SCHUMACHER, P. MACKWOOD, S. B. FLORESCO; Psychology and Ctr. for Brain Hlth., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Human and animal research highlight the contributions of the neuropeptide, corticotropin-releasing factor (CRF), in physiological and behavioural responses during stress. In humans, elevated plasma CRF levels are observed in stress-related disorders, characterized by

cognitive impairments and motivational deficits, including a reduced willingness to pursue rewarding stimuli. In rats, acute restraint stress reduces preference for larger rewards associated greater effort cost, without affecting the incentive value of large rewards. These effects are driven in part by increased CRF transmission, as they were blocked by CRF antagonists and recapitulate by treatment with exogenous CRF. Yet, the endogenous CRF pathways that may perturb effort-related decision and motivation remains unclear. One possible candidate is the bed nucleus striatum terminalis (BNST), a region of the extended amygdala that is activated under stressful conditions and BNST CRF cells project to key nodes within the mesocorticolimbic reward system. Here, we examined whether excitation of BNST CRF neurons is sufficient to drive motivational deficits observed during stress. Adult Long Evans rats were trained on an effort discounting task where they chose between a low effort/small reward option that requires 1 lever press for the reception of 1 pellet, or a high effort/high reward (HR) option that requires a set number of presses (1, 5, 10, 20) to obtain a larger, 4-pellet reward, with the effort requirement increasing across blocks within a session. Acute chemogenetic excitation of CRF- BNST neurons with clozapine-*N*-oxide (CNO) reduced preference for the HR option in both males and females. This effect was more pronounced in animals that exhibited greater baseline motivation to work for effortful large rewards. These findings show that hyperactivity of BNST CRF neurons is sufficient to recapitulate the reduced willingness to expend effort for high value rewards seen after stress. This adds to a growing body of literature that implicates elevated central CRF signalling in stress-induced alterations in reward processing.

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Poster

PSTR482: Decision-Making

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Program #/Poster #: PSTR482.08/T4

Topic: H.03. Decision Making

Support: CIHR grant (PJT-162444)

Title: Dopaminergic and Orbitofrontal Modulation of Cue-Guided Delay Discounting

Authors: *L. T. NOTTE[1], M. ZHAO[2], S. B. FLORESCO[1];
[1]Psychology and Ctr. for Brain Hlth., Univ. of British Columbia, Vancouver, BC, Canada;
[2]Psychology and Ctr. for Brain Hlth., Univ. of British Colombia, Vancouver, BC, Canada

Abstract: Adaptive cost/benefit decision-making requires tuning of one's subjective value of an outcome to the cost of obtaining it. Devaluation of rewards when they are delayed is observed in humans and animals and can be studied in rodents using delay discounting procedures, where animals choose between an immediate/small reward, and a larger/delayed reward, and delay length changes systematically across a session. By sampling options, animals form internal

representations of changing delay lengths to guide choice, and selection of the immediate/small reward is interpreted as a measure of impulsive choice. Choice on these tasks is altered by manipulations of dopaminergic transmission and the lateral orbitofrontal cortex (lOFC). In real life, however, delays are often signaled by environmental cues (e.g., queues when deciding where to eat at a festival). Yet, how these systems may differentially influence choice under conditions where delays are cued is unclear. Here, we used a novel cue-guided delay discounting task. At the start of each trial, an auditory cue was presented to inform male and female rats of whether the delay of obtaining the large reward is short (1s) or long (30s). After ~3 weeks of training, rats developed stable preference for the large/delayed or immediate/small rewards on short- or long-delay trials, respectively. Blockade of either dopamine D1(SCH23390; 0.01-0.03 mg/kg) or D2 receptors (eticlopride; 0.03-0.09 mg/kg), did not affect choice on this task, revealing that dopamine signaling does not mediate cued delay discounting under normative conditions. In comparison, treatment with amphetamine (0.5 mg/kg) increased impulsive choice. This effect was blocked by D_1 or D_2 antagonists in males, suggesting that impulsogenic effects of amphetamine were driven by activation of dopamine receptors. Bilateral inactivation of the lOFC induced a trend to shifting choice profiles in a delay-dependent manner, wherein rats were less likely to choose the large/delayed reward on short-delay trials, and more likely to do so on long-delay ones. lOFC inactivation also increased choice latency. These findings provide a preliminary insight into differences in neural systems mediating delay discounting guided by internal information vs external cues.

Disclosures: L.T. Notte: None. **M. Zhao:** None. **S.B. Floresco:** None.

Poster

PSTR482: Decision-Making

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Program #/Poster #: PSTR482.09/T5

Topic: H.03. Decision Making

Support: NIH Grant DA025634
NIH Grant AA026577

Title: Brain stimulation reward supports high reward discrimination and choice stability in temporal discounting, progressive ratio, and probabilistic discounting decision-making tasks

Authors: *J. D. ROITMAN[1], J. P. SEVIGNY[2], D. MCANDREW[1], S. PATEL[1], R. M. DONKA[2];
[2]Psychology, [1]Univ. of Illinois Chicago, Chicago, IL

Abstract: Studies of decision-making in rodents typically deliver high-value food rewards such as sugar pellets. However, food deprivation is necessary to ensure motivation to engage in a task, with engagement declining across the session as satiety develops, potentially altering choice. We sought to remedy these challenges by using brain stimulation reward (BSR), a highly

discriminable and non-satiating reinforcer, in multiple decision-making tasks. Long-Evans rats were implanted with stimulating electrodes in the medial forebrain bundle at the level of the lateral hypothalamus and were trained to lever press for stimulation. Using a rate-frequency protocol, we determined the range of stimulation frequencies that elicited threshold (theta, 0%) and maximal (alpha, 100%) responding. We conducted magnitude discrimination training between pairs of frequencies assigned as 'small' and 'large' rewards (e.g. 25% vs. 95% of alpha). Standard rewards were administered as five 500ms stimulation trains. We then tested decision-making in temporal discounting, progressive ratio, and probabilistic discounting tasks. To assess temporal discounting, subjects chose between a larger-later (95%) and a smaller-sooner (50%) reward. Within each session, five blocks were presented with increasingly longer delays (1, 2, 4, 8, 12 s). Subjects demonstrated a highly consistent declining preference for the larger-later reward when delays were 4 s or greater. Progressive ratio task behavior was tested on schedules that varied effort (high or low) across three reward levels (95%, 50%, or 25%). For each reward level, rats earned significantly more rewards in the low- compared to high-effort schedule. Across reward frequencies, there were no differences between 95% and 50% levels, but significantly fewer rewards were obtained for the 25% reward. In probabilistic discounting tasks, subjects chose between a large-risky and small-certain reward. Within each session, five blocks were presented with decreasing large-risky reward probability (p=1.0, 0.8, 0.6, 0.4, 0.2). When large and small rewards were assigned as different frequencies (e.g. 95%/0% vs. 25%), subjects demonstrated indifference between the options regardless of the frequencies selected. When stimulation frequency was held constant and large and small were assigned as different numbers of stimulation trains (e.g. 5/1 vs. 3), subjects showed a declining preference for the large-risky reward as probability decreased. Ultimately, results from all three tasks support the use of BSR in decision making. BSR avoids issues with food reward while supporting a high level of discrimination and motivation.

Disclosures: J.D. Roitman: None. **J.P. Sevigny:** None. **D. McAndrew:** None. **S. Patel:** None. **R.M. Donka:** None.

Poster

PSTR482: Decision-Making

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Program #/Poster #: PSTR482.10/T6

Topic: H.03. Decision Making

Support: NSF 1703340

Title: Explore-exploit behavior in rodents and humans using the changing bandit task

Authors: C. CAPOZELLA[1], S. BERGSTROM[2], H. XIONG[3], S. WANG[4], R. C. WILSON[2], *J.-M. FELLOUS[5];
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Abstract: Explore-exploit behavior is the decision-making process on whether to explore new options without the certainty of their consequences or to exploit familiar options known to have predictable outcomes. This behavior is critical for organisms to survive and thrive when navigating the world around them, but how is an optimal balance achieved between these decision-making tendencies? We address this question using the same changing bandit task in rats and humans. In the changing bandit task, a subject is asked to choose between two options with *a priori* unknown rewards/outcomes. The reward amount associated with each option changes probabilistically at different, constant hazard rates unknown to the subject, such that the consistency/likelihood of a reward amount across consecutive trials differs for each option. We hypothesize that rats and humans will learn to switch options (explore) after the lowest reward amount is dispensed especially if the hazard rate is high, and will persist if the option yields the highest reward especially if the hazard rate is low. The Brown Norway rats included both males and females. They were placed on a maze where they first had go to an unrewarded "home base" before two feeders opposite the home base started blinking, indicating reward availability. Rats probabilistically received either zero, one, or three drops of a sucrose solution from these feeders, with one feeder having a higher hazard rate than the other. Preliminary analysis of the data show that both male and female rats are more likely to exploit the highest rewarding feeder than the reliable but less rewarding one and seem to display more exploitative behaviors with time. A MATLAB-based GUI was used for the human subjects to mimic the changing bandit task using a point-based reward system. The interface displays push buttons designed to represent the two feeders and home position of the rat experiment with the same rewards and hazard rate. Human subjects experienced the exact same series of decisions as the rats. Human participants performed two sessions, one with different hazard rates and one of three control conditions. Each session included 350 decisions to try and obtain the highest number of points possible. Decisions, reaction times and computer mouse tracking data were collected. Initial results from seven participants indicate that humans and rats are qualitatively comparable. Additionally, compared to rats, while humans are more likely to exploit the highest rewards, they do so more consistently with lower hazard rates. Additional human and rat participants are being recruited to draw more conclusions about the similarities/differences between the two species.

Disclosures: C. Capozella: None. **S. Bergstrom:** None. **H. Xiong:** None. **S. Wang:** None. **R.C. Wilson:** None. **J. Fellous:** None.

Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.11/T8

Topic: H.03. Decision Making

Support: UCLA-HSI SOMA Summer REU

Title: Methamphetamine reduces the duration of foraging bouts in rats performing a naturalistic decision-making task

Authors: *A. K. GARCIA, R. K. KENDALL, A. M. WIKENHEISER;
Psychology, UCLA, Los Angeles, CA

Abstract: Knowing when to abandon a depleting food source is critical for efficient foraging. Persisting for too long with a dwindling resource may mean missing out on better opportunities elsewhere, while abandoning locations too readily may mean spending too much time searching for better options. One prominent theoretical model proposes that tonic dopamine levels encode the average rate of reward in an environment, a critical determinant of how long to persist with a food source at hand. Here, we test whether increasing dopamine levels via administration of methamphetamine decreases persistence with potential food sources, in line with theoretical models of dopamine function. Rats performed a spatial foraging task in which they earned food from two distinct foraging patches. Within each patch, the rate of food delivery decreased over time following an experimenter-controlled schedule. The travel cost of switching between patches was manipulated by imposing a delay between leaving one patch and entering another. Before each session, rats were administered methamphetamine (1 mg/kg) or a control saline injection. Our main behavioral measure of interest was how long rats persisted on visits to each foraging patch. Consistent with theoretical models of foraging behavior, rats remained longer in patches with slower depletion rates, and remained longer in all patches when the travel cost was high. Methamphetamine caused a significant reduction in patch residence duration relative to saline sessions. Importantly, methamphetamine did not alter rats' sensitivity to travel cost or patch depletion rate. However, methamphetamine significantly reduced rats' consumption of food pellets, and strongly affected the way rats moved. Compared to saline injections, methamphetamine first decreased, but over sessions came to increase, the amount of time that rats spent stationary or moving at very slow speeds. Methamphetamine increased rats' running speed during bouts of movement and increased thigmotaxis. Together, these data are consistent with a role for dopamine in encoding average rate of reward, but more specific manipulations will be necessary to disentangle the motivational, motor, and decision-making functions of dopamine release.

Disclosures: A.K. Garcia: None. **R.K. Kendall:** None. **A.M. Wikenheiser:** None.

Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.12/T9

Topic: H.03. Decision Making

Support: NIH Grant GR040336
NIDA Grant P30 DA048736
University of Washington

Title: Psilocybin administration improves behavioral flexibility after opiate withdrawal on a complex strategy switching task

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Univ. of Washington, Seattle, WA

Abstract: The rising prevalence of opioid addiction in both recreational and medical users is associated with a significant increase in drug-related mortality and morbidity in the U.S (Kolodny et al., 2015). Opiate use disorder (OUD) impairs flexible and goal-directed behaviors in both animals and humans (Halbout et al., 2023). By focusing on how to improve behavioral flexibility, we hope to find a treatment that can significantly help patients replace their maladaptive responses with more appropriate, non-addictive choices. One drug that could assist in improving behavioral flexibility is psilocybin, which has shown efficacy in treating depression, alcoholism, and nicotine addiction with a rapid-acting and non-addictive profile (Bogenschultz et al., 2015, Johnson et al., 2014, Carhart-Harris et al., 2017). To explore the effects of psilocybin on behavioral inflexibility in OUD, we used a new behavioral paradigm that assesses the flexible use of different behavioral strategies (Miles et al., 2024) as rats are undergoing morphine withdrawal and subsequent psilocybin treatment. The task is performed on a fully automated plus-maze and consists of 2 strategy types: place and alternation. In the place strategy block, rats must select the same reward arm on all trials regardless of start location; in the alternation strategy block, rats must select alternating reward arms, again regardless of start location. Three strategy switches were tested for each maze session. Pre-trained Long-Evans rats (n=9) completed baseline trials (day 0) on the task, then underwent twice-daily morphine (10mg/kg, SC, n=7) or saline (1mL/kg, SC, n=2) injections for 10 days (days 1-10). On day 11, morphine was withheld to induce spontaneous withdrawal. Treatment (day 12) consisted of either psilocybin (1mg/kg, SC, n=4), or saline (1mL/kg, SC, n=5). Task performance was measured on each of these days, as well as five days post treatment (day 17). Sucrose preference and general activity-related open-field behavior were also measured. Initial analyses show that opiate withdrawal decreases the rats' ability to flexibly adopt new spatial strategies when the reward contingencies shift (relative to the baseline condition). Importantly, rats that received psilocybin treatment after opiate withdrawal consistently exhibited increased flexibility compared to saline-treated rats. Also, while sucrose preference decreased during morphine withdrawal, psilocybin treatment rescued sucrose preference. In summary, these preliminary data support the use of psilocybin to remedy opiate withdrawal symptoms, specifically the observed decrease in flexibility.

Disclosures: V.I. Hones: None. **M. Bottoms:** None. **S.J.Y. Mizumori:** None.

Poster

PSTR482: Decision-Making

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR482.13/T10

Topic: H.03. Decision Making

Support: NIH P50 Grant 1P50MH132642-01
NIH K99 Grant 7K99MH129613-02

Title: Prefrontal transthalamic processing of uncertainty drives cognitive flexibility

Authors: N. H. LAM[1], ***A. MUKHERJEE**[1], R. WIMMER[1], M. R. NASSAR[2], Z. CHEN[3], M. HALASSA[1];
[1]Neurosci., Tufts Univ., Boston, MA; [2]Neurosci., Brown Univ., Providence, RI; [3]Dept. of Psychiatry, New York Univ., New York, NY

Abstract: Real world decisions are often made in environments whose features are noisy and uncertain, leading to errors. Therefore, to increase the success of our decisions the brain needs to appropriately account for the degree and the different sources of uncertainty in the environment. Theoretical work has shown that hierarchical estimates of uncertainty and its sources can be rapidly combined to adapt to changing environments.
While the neural circuit mechanisms through which the brain generates uncertainty estimates and uses them for adaptive decision making remains an open question, recent studies have found that interactions between the frontal cortex (FC) and the medio dorsal thalamus (MD) are crucial for decision making under cue input uncertainty. Here, to interrogate MD-FC interactions in decisions involving multiple sources of uncertainty, we utilized the tree shrew, *Tupaia belangeri*. Through *in vivo* electrophysiological recordings in *Tupaia* subjects performing a hierarchical decision task with covert reversals in task rules, we found that the MD maintains cueing and context uncertainty as independent representations. This segregation allows the relevant thalamic population to drive FC circuit reconfiguration following a reversal by appropriately attributing errors to an environmental change. Further dissection of the hierarchical decision task revealed a transthalamic pathway for anterior cingulate cortical error monitoring to reconfigure prefrontal executive control. Collectively, our work highlights a potential role for the thalamus in demixing cortical signals while providing a low dimensional pathway for cortico-cortical communication.

Disclosures: N.H. Lam: None. **A. Mukherjee:** None. **R. Wimmer:** None. **M.R. Nassar:** None. **Z. Chen:** None. **M. Halassa:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.01/T11

Topic: H.04. Executive Functions

Support: R01MH131559

Title: Both stimulus-control state associations and stimulus-response associations contribute to item-specific proportion congruency effect

Authors: *B. HUANG, J. NICHOLSON, T. LOOI, Y.-Y. CHENG, Q. HONG, J. JIANG; Univ. of Iowa, Iowa, IA

Abstract: Both stimulus-control state associations and stimulus-response associations contribute to item-specific proportion congruency effectDr. Bingfang Huang[1] (bingfang-huang@uiowa.edu), Jordan Nicholson[1], Tommy Looi[1], Yong-Yao Cheng[1], Qiutong Hong[1], Dr. Jiefeng Jiang[11]University of IowaCognitive control coordinates our thoughts and actions with internal goals. The cognitive control system is adaptive when conflict conditions change. Item-specific proportion congruent (ISPC) effect is a classic phenomenon of the adaptative conflict effect. It means when participants unconsciously experience 50% congruent condition and 50% incongruent condition overall while mostly congruent (MC) condition for one set of stimuli and mostly incongruent (MI) condition for another set of stimuli, the conflict effect (i.e., performance in incongruent condition compared to congruent condition) in the MI condition decreases compared with that in the MC condition. Many studies have been done to explore the mechanisms of the ISPC effect. ISPC effect is believed to be triggered by the learning of the stimulus-control state (SC) associations and/or contingency learning of the stimulus-response (SR) associations. The current consensus is that SC and SR associations learning will dominate the ISPC effect under different situations. However, it is currently unknown whether the learning of both SC and SR simultaneously contribute to the ISPC effect. We try to address this question by decoding the SC and SR associations from Electroencephalogram (EEG) data in a 4-key Stroop task with ISPC manipulations (n = 19). The behavioral results repeated the classic ISPC effect. Preliminary EEG results showed both SC and SR associations can be decoded early following stimulus onset. Therefore, our study provides initial evidence for concurrent contributions of SC and SR learning in cognitive control.

Disclosures: B. Huang: None. **J. Nicholson:** None. **T. Looi:** None. **Y. Cheng:** None. **Q. Hong:** None. **J. Jiang:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.02/Web Only

Topic: H.04. Executive Functions

Support: CONAHCYT 1269044

Title: Cognitive flexibility in mice: effect of fixed or variable change and continuous or variable reinforcement

Authors: *A. OROZCO COLES[1], T. V. CAMPOS ORDONEZ[2], J. BURITICÁ[1]; [1]Ctr. de Estudios e Investigaciones en Comportamiento, Univ. of Guadalajara, Guadalajara, Mexico; [2]Ctr. Universitario de Ciencias Biológicas y Agropecuarias, Univ. of Guadalajara, Zapopan, Mexico

Abstract: Behavioral flexibility is the ability of human and non-human animals to adapt to environmental changes through response change. The Midsession Reversal Task (MSR) measures this type of flexibility. Studies report that strategies to adapt to MSR depend on the task and the species: 1) timing and 2) win stay/lose shift. Mice's performance in this procedure is yet unknown. The objective of this study was to analyze mice's performance in an MSR task with fixed (midsession) and variable reversal changes, as well as continuous (100%) or variable (50%) reinforcement. Sixteen CD1 mice were exposed to three phases with a Fixed Ratio 1 schedule. They were deprived of water. Condensed milk diluted in water was used as a reinforcement. The procedure in the first phase was a fixed reversal change with continuous reinforcement (F100). Then, in the second phase a reversal change was variable, and the reinforcement was continuous (V100). Lastly, the reversal change was variable in the third phase, as was the reinforcement (V50). For half the subjects, the order of phases 1 and 2 was reversed. Preliminary results suggest the use of both strategies. The behavior was controlled by the contingency to which they were exposed. Intra-session analyses show both anticipation and perseveration errors, mostly in variable phases. These latter errors could suggest deficits in reversal learning via working memory or alternatively, the use of a strategy such as timing for task solution.

Disclosures: A. Orozco Coles: None. **T.V. Campos Ordonez:** None. **J. Buriticá:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

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Program #/Poster #: PSTR483.03/T12

Topic: H.04. Executive Functions

Support: AFOSR grant number 20RHCOR04

Title: Vagus Nerve Stimulation Effects on Memory Acquisition and Consolidation in Male and Female Rats.

Authors: *B. SHARMA[1,2], K. A. JONES[1,3], L. OLSEN[4], C. N. HATCHER-SOLIS[1];
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Abstract: Vagus nerve stimulation (VNS) modulates key cognitive processes including memory acquisition and consolidation. Our previous findings showed a single 30-minute session of VNS during the memory consolidation phase significantly enhanced recognition memory and aversion learning in male rats. We extended the same VNS parameters to investigate if VNS during memory acquisition had a similar effect in male rats. Additionally, we examined the effects of VNS on cognition during memory acquisition or consolidation in female rats. Male and female Sprague-Dawley rats underwent surgical implantation of platinum/iridium electrodes around the

left cervical branch of the vagus nerve (VN) under anesthesia. Following a 10-day recovery period, rats were divided into sham and VNS groups. Female rats were further categorized into diestrus or estrus phase based on the analysis of vaginal wet smears on the testing day. Behavioral assessments included the elevated zero maze (EZM) for anxiety-like behavior, novel object recognition (NOR) for recognition memory, and passive avoidance test (PAT) for aversion learning and memory. The experiment design involved stimulating the VN with 100 μs biphasic pulses, 30 Hz, 0.8 mA stimulation for 30 minutes during memory acquisition or consolidation (i.e., before or after behavior, respectively). VNS in male rats before training did not affect anxiety-like behavior, recognition memory, or aversion learning and memory. However, in female rats, VNS before training acted as an anxiolytic intervention (sham: n=13, VNS: n=15; $p<0.05$), but this effect was not significant when analyzed based on estrous cycle phase. VNS before training also significantly decreased aversion learning in females during the estrus phase (sham: n=8, VNS: n=7; $p<0.05$) but not in diestrus. Moreover, VNS after training in females did not enhance recognition memory, with consistent results across estrous cycle phase. While there was no improvement in aversion learning among all females or females in estrus phase, those in diestrus phase showed significantly better performance compared to sham (sham: n=8, VNS: n=15; $p<0.05$), indicating estrous cycle mediates the effect of VNS on PAT performance. These findings emphasize the importance of VNS during memory processes in rats and the influence of the estrous cycle, suggesting a need for further molecular studies to understand these effects.

Disclosures: B. Sharma: None. **K.A. Jones:** None. **L. Olsen:** None. **C.N. Hatcher-Solis:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.04/U1

Topic: H.05. Working Memory

Support: NIH EY033925
NIH EY016407
NIH 5T32EY007136

Title: Prefrontal cortex controls the strategic allocation of working memory resources

Authors: *N. TARDIFF[1], G. E. HALLENBECK[1], T. C. SPRAGUE[3], C. E. CURTIS[1,2]; [1]Dept. of Psychology, [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Dept. of Psychological and Brain Sci., UC Santa Barbara, Goleta, CA

Abstract: The capacity-limited nature of working memory presents an optimization problem: if multiple items need to be remembered, how should resources be allocated to maximize performance? When some items are more crucial for recall than others, people prioritize items according to their relevance, resulting in better memory for prioritized items but worse memory

for other items (e.g., Yoo et al., 2018). In visuospatial working memory, high-priority items are encoded with higher gain than low-priority items in early visual areas thought to store the memoranda, as measured by BOLD fMRI (Yoo et al., 2022). In contrast, trial-by-trial amplitudes of delay-period activity in the superior precentral sulcus (sPCS) of the frontal cortex predict prioritization in visual cortex, though sPCS activity does not show a gain effect (Li et al., 2024; Yoo et al., 2022). These findings suggest a division of labor: visual regions may store the prioritized representations, while sPCS serves as a control region, implementing prioritization by sculpting the gain in visual cortex.

To causally test the role of frontal cortex in the allocation of working memory resources, we used transcranial magnetic stimulation (TMS) to disrupt activity in the sPCS of human subjects during the delay period of a two-item memory-guided saccade task (N = 14, 9 female). Priority was manipulated by pre-cueing subjects as to which of the two items was more likely to be probed after the delay (the high-priority item). TMS was stereotaxically targeted to the left sPCS, which was identified in individual subjects using an fMRI-based retinotopic mapping procedure (Mackey et al., 2017). If sPCS is involved in prioritization, memory error for the high- and low-priority items should be more similar after TMS. Alternatively, if sPCS is involved in memory storage, TMS should increase errors for both items.

Replicating our previous findings, memory error was significantly lower for the high compared to the low-priority item when no TMS was applied. TMS to sPCS made memory errors more similar for high- and low-priority items, but this difference was driven by reduced error for low-priority items. To identify if this pattern of results was more consistent with an effect of TMS on prioritization or storage, we fit a computational model of memory resource allocation to subjects' data. Confirming our hypothesis that sPCS controls prioritization, the model indicated that subjects allocated their memory resources more uniformly between the items after TMS. The total amount of modeled memory resources was also affected by TMS. In sum, our results provide causal support for the hypothesis that sPCS controls information in memory.

Disclosures: N. Tardiff: None. **G.E. Hallenbeck:** None. **T.C. Sprague:** None. **C.E. Curtis:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

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Topic: H.05. Working Memory

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Title: Neural mechanisms of resource allocation in working memory

Authors: *H.-H. LI[1,2], T. C. SPRAGUE[3,2], A. H. YOO[4], W. MA[4], C. E. CURTIS[4];
[1]The Ohio State Univ., Columbus, OH; [2]New York University, New York, NY; [3]Psychological and Brain Sci., UC Santa Barbara, Goleta, CA; [4]New York Univ., New York, NY

Abstract: A signature of working memory (WM) is that it has severe limitations in its capacity. The precision of WM reports declines steeply as the number of items being stored increases. To mitigate capacity limits of working memory, people allocate resources according to an item's relevance. However, the neural mechanisms supporting such a critical operation remain unknown. We investigated the neural mechanisms for allocating working memory resource by a memory-guided task, in which human participants were required to hold the locations of two items in their WM. The two items were cued to have different priority levels, manipulated by the probability that an item would be probed at the end of the trial. We developed computational neuroimaging methods to decode and demix two items held in WM from fMRI activity patterns. By fitting an encoding model to the BOLD responses, we found that in early visual and high-level dorsal visual cortex, items that were more relevant for the task were associated with higher neural gain. By applying a Bayesian decoder, we found that the content (locations) of two items concurrently held in WM can be decoded in visual cortex and parietal cortex, with the higher-priority memorandum decoded with smaller error and lower uncertainty. Importantly, the neural prioritization, quantified as the difference in decoded precision between the two items, predicted behavioral prioritization, quantified as the difference in the magnitude of memory error between the two items. Lastly, to identify the brain regions that control the allocation of WM resource, we conconducted a whole-brain GLM using the neural prioritization as the regressor. We found that trial-wise variability in the magnitude of delay activity in frontal cortex correlated with the differences in decoded precision between low and high priority items in visual cortex. These results suggest a model in which feedback signals broadcast from frontal cortex sculpt the gain of memory representations in visual cortex according to behavioral relevance, thus, identifying a neural mechanism for resource allocation.

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Poster

PSTR483: Roles of Memory in Cognitive Flexibility

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.06/U3

Topic: H.05. Working Memory

Support: NIH Grant R01 EY034118

Title: High resolution imaging of the human prefrontal cortex during working memory

Authors: *Z. LU[1,2], L. T. DOWDLE[4], K. N. KAY[5], C. E. CURTIS[3];
[2]Psychology, [3]Psychology & Ctr. for Neural Sci., [1]New York Univ., New York, NY;
[4]Neurosciences, Univ. of Minnesota, Minneapolis, MN; [5]Radiology, Univ. of Minnesota, Twin Cities, St Paul, MN

Abstract: Working memory (WM) increases the duration with which stimulus representations are available for further processing. The canonical theory of WM posits that persistent activity in neurons in lateral prefrontal cortex (PFC) stores WM representations. While electrophysiological data from nonhuman primate studies supports this hypothesis, data from fMRI studies have largely failed to find persistent activity in human lateral PFC. One possible explanation for this puzzling discrepancy stems from recent analyses of the anatomical distribution of neurons tuned to stimulus features across macaque PFC. Namely, the resolution of previous fMRI measurements may be too coarse relative to the fine-grained spatial scales of tuned neurons. To address this potential limitation, we used high-resolution (900 micron isotropic voxels) fMRI at 7T to measure delay period activity during a memory-guided saccade task within a partial slab covering lateral PFC (N=5; TR 2100 ms, 60 slices, partial Fourier 6/8, in-plane acceleration 2, multiband acceleration 2). Custom pre-processing methods were implemented to achieve high spatial accuracy, including EPI undistortion, head motion correction, and run-wise nonlinear anatomical co-registration. We also performed population receptive field mapping to identify topographically organized visual field maps and spatially selective voxels. We find robust persistent activity and strong decoding of memoranda from visual field maps in the superior and inferior precentral sulcus. Although preliminary, we find no such evidence in more anterior portions of the PFC. These results suggest that high-field fMRI with sub-millimeter spatial resolution can help bridge the gap between nonhuman primate neurophysiology and human neuroimaging research.

Disclosures: Z. Lu: None. **L.T. Dowdle:** None. **K.N. Kay:** None. **C.E. Curtis:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.07/Web Only

Topic: H.04. Executive Functions

Title: The impact of physical activity on cognitive function

Authors: *M. GUTIÉRREZ-MUÑOZ, X. ORTIZ;
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Abstract: Among the benefits of physical activity are cognitive benefits; an increasing number of studies have supported the idea that physical activity enhances these executive functions. Furthermore, it may have a positive effect on attention and processing speed. The aim of the present study was to assess the impact of a physical activation program on cognitive functions in

sedentary adults. Thirty-one participants (20 males and 11 females) underwent cognitive assessment before the 10-week physical activity program and after its completion. The results showed improvements in post-intervention outcomes; significant differences were found in performance on the MOCA test ($p<0.01$), phonological verbal fluency ($p<0.01$), and processing speed ($p<0.01$). These findings provide evidence for the importance of physical activity for optimal cognitive functioning.

Disclosures: M. Gutiérrez-Muñoz: None. **X. Ortiz:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

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Program #/Poster #: PSTR483.08/U4

Topic: H.04. Executive Functions

Support: NIMH Grant R01MH122613
1S10OD025025-01

Title: Integration of internal and external sources of information to guide cognitive control

Authors: *S. LEACH[1], H. MORROW[2], J. JIANG[3], K. HWANG[1];
[1]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA; [2]Univ. of Iowa, Iowa City, IA; [3]Psychological & Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: To flexibly guide behavior, the human brain must integrate multiple streams of information from many diverse sources that can be externally presented or internally maintained. The frontoparietal network has long been assumed to be involved in integrative functions due to the large number of hub (i.e., highly connected) regions. Nevertheless, how cognitive representations in these regions support integration is not yet fully understood. We utilized a Bayesian generative model to suggest a framework where integration is achieved by creating a joint distribution that encodes multiple task-relevant features to guide goal-directed behavior. In this framework, the statistical properties of this joint distribution can indirectly measure the degree of integration. We collected functional magnetic resonance imaging (fMRI) data from 39 participants who performed a paradigm requiring the integration of perceptual (color) information with non-observable state information to select the correct task-to-perform for each trial. In this paradigm, each trial began with an array of red and yellow dots. Participants had to determine if there were more red or yellow dots. The non-observable state was the mapping between color (red or yellow) and task (face or scene). A change in state meant flipping this mapping between color and task. The Bayesian generative model was used to estimate on a trial-level basis each participant's probabilistic belief in the non-observable state, dominant color perception, and task-to-perform. Critically, the model integrates the two probabilistic distributions of state and color information into a joint distribution to encode the correct task-to-perform. We utilized trial-level representational similarity analysis (RSA) to identify brain

regions encoding externally presented perceptual information versus non-observable state information. In addition to this, we used RSA to identify brain regions encoding/maintaining the representation of the task to-perform, inferred from the integrated product of these two independent sources of information. Frontoparietal regions showed greater similarity profiles between trials where the dominant color was the same and ambiguity was similar. Frontoparietal hub regions showed greater similarity profiles between trials where the hidden states were the same and uncertainty in the hidden state was similar. Finally, the task to-perform showed primary motor and parietal regions. Our results support a framework where the integration of observable and non-observable information is achieved by creating a joint distribution encoding multiple task-relevant features.

Disclosures: S. Leach: None. **H. Morrow:** None. **J. Jiang:** None. **K. Hwang:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.09/U5

Topic: H.04. Executive Functions

Support: R01MH131559

Title: Prediction Error Signals of Context-Task Demand Association

Authors: *Q. HONG[1], G. YANG[2], J. JIANG[3];
[1]Psychology and Brain Sci., Univ. of Iowa, IOWA CITY, IA; [2]Psychology and Brain Sci., Univ. of Iowa, Iowa, IA; [3]Psychological & Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: A previous study (Jiang et al., 2020) discovered that hippocampal representations of spatial context is correlated with the memory retrieval of its associated task demand. However, as the retrieved task demand is not always a correct match of the actual task demand, how the retrieved task demand affects following task execution remains, and how their discrepancy (i.e., prediction error) drives the learning of context-task demand association remains unclear. To address these questions, we reanalyzed the same data from Jiang et al. (2020), focusing on prediction error signals of retrieved task demand. This fMRI experiment adopted a 3D virtual environment where participants navigated themselves to four distinct houses (i.e., contexts) within the fMRI scanner, each house associated with different possibilities (25% and 75%) for receiving two different tasks (i.e., task demands). We first conducted univariate general linear model (GLM) analysis to locate prediction error signals. We observed that during the execution of task, higher fMRI activation level for unexpected than expected task demands mainly in the visual cortex. This suggests online adjustment of task representation due to inaccurate prediction of retrieved task demand. We also measured multivariate pattern similarity 1) between predicted task and predicted task, 2) between predicted task and unpredicted task, and 3) between unpredicted task and unpredicted task. We then compared the pattern similarity measures to

investigate multivariate prediction error representations. We found that the highest pattern similarity differences are between the predicted-predicted task similarity and the unpredicted-unpredicted task similarity in frontal eye fields, anterior cingulate cortex (ACC), lateral temporal cortex, and dorsal stream visual ($p < 0.01$ uncorrected). Together, our findings provided initial evidence of both univariate and multivariate task demand prediction errors. Future analysis will test 1) how prediction error signals in the visual cortex influence task performance and 2) how prediction error patterns in the ACC affect the learning and updating of context-task demand association

Disclosures: Q. Hong: None. **G. Yang:** None. **J. Jiang:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.10/U6

Topic: H.04. Executive Functions

Support: Center on Compulsive Behaviors Postdoctoral Fellowship

Title: Examining the role of memory in context-dependent decisions using human intracranial recordings

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Abstract: We rely on our memory and past experiences to guide behavior. In some cases, however, competing memories may elicit uncertainty that interferes with effective decision-making. Context-dependent decisions are those in which the appropriate response differs across contexts, requiring flexible behavior and memory to select the correct response for a given context. The current study examines how memory contributes to context-dependent decisions. We recorded neural activity intracranially from the human temporal lobe in medication resistant epilepsy patients as they performed a memory decision task. The task required patients to learn the appropriate decision between arbitrary categories (cutlery vs. animals and houses vs. faces). These decisions were experienced in two different contexts (beach vs. forest). Importantly, for one decision pair, the decision was context dependent, meaning the correct response differed between the two contexts. We found that patients were slower and less accurate when performing context-dependent decisions compared to context-free decisions. We posit that these behavioral effects may result from the demand for selective memory retrieval during context-dependent decisions. Preliminary analyses show modulations in theta power in the temporal lobe, a neural correlate previously associated with memory retrieval, during context-dependent

decisions. Ongoing analyses seek to better understand the relationship between memory processes and flexible decision-making.

Disclosures: K. Sundby: None. **S. Lopez-Guzman:** None. **K.A. Zaghloul:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.11/U7

Topic: H.05. Working Memory

Support: DFG JA 1999/6-1

Title: Single neuron correlates of working memory maintenance and flexible retrieval in the human lateral prefrontal cortex

Authors: *H. CHEN[1,2,3], L. SCHIFFL[1,2], L. M. HELD[1,2], G. ALKAN[1,2], P. FAVERO[1,2], A. WAGNER[2], B. MEYER[2], J. GEMPT[4], S. N. JACOB[1,2];
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Abstract: Working memory, the temporary storage and manipulation of task-relevant information, is a crucial cognitive function of the prefrontal cortex (PFC). It serves as the basis for cognitive flexibility, which allows for making adaptive decisions based on the current context within a changing environment. However, it remains unclear how information is maintained in working memory together with the context it appeared in, and how information is retrieved from working memory in a context-dependent manner. Here, we recorded large-scale spiking activity (n = 799 well-isolated single neurons) from a subject with planar microelectrode arrays chronically implanted in the right middle frontal gyrus (MFG) and inferior frontal gyrus (IFG). Each prefrontal region was implanted with one 64-channel array. Neuronal data acquisition proceeded while the subject performed two multiple-item delayed match-to-sample working tasks with retro-cueing. These tasks required the subject to memorize two sample stimuli, presented either sequentially (temporal context, TC) or simultaneously (spatial context, SC), and retrieve one of the two samples indicated by a retro-cue for comparison with a test stimulus. Numerical quantities served as stimuli and were presented in either non-symbolic notation (sets of dots, numerosities) or symbolic notation (digits, Arabic numerals). All numerical stimuli and retro-cues were controlled for the influence of low-level visual properties. Behavioral analyses demonstrated that the subject's task performance was comparable to that of healthy controls, exhibiting classic behavioral signatures of numerical cognition including the size effect and the distance effect. Neuronal analyses showed that the large majority of recorded neurons was task-

modulated (n = 636; 79 %), i.e. their activity changed in the course of TC or SC trial epochs. Almost half of the recorded neurons were modulated in both tasks (n = 372; 46 %). Notably, we found a significant proportion of neurons in both MFG (n = 132; 16 %) and IFG (n = 88; 11 %) that were tuned to number in the epochs of sample presentation or sample memory. More neurons were tuned to non-symbolic number (n = 181 across MFG and IFG; 22 %) than to symbolic number (n = 67; 8 %). Only a small subset of neurons was tuned to both notations (n = 28; 3 %). Ongoing analyses are directed at investigating whether distinct populations of neurons encode numerical information in different contexts (first or second, left or right) and after cueing during memory retrieval.

Disclosures: H. Chen: None. **L. Schiffl:** None. **L.M. Held:** None. **G. Alkan:** None. **P. Favero:** None. **A. Wagner:** None. **B. Meyer:** None. **J. Gempt:** None. **S.N. Jacob:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.12/U8

Topic: H.04. Executive Functions

Support: R01 NS102201

Title: Action errors lead to working memory suppression: Bayesian hierarchical mixture modeling and the contralateral delay activity

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Abstract: The ability to detect errors and adapt to errors is a crucial aspect of cognitive control, yet the underlying processes remain debated. The recent adaptive orienting theory (AOT) posits that an action error triggers a cascade of processing that begins with a broad suppression of motoric and cognitive processes followed by attentional reorienting towards the source of the error. This suggests that action error commission would be detrimental to ongoing cognitive processes. In our previous study (Wessel, Jiang et al., 2022), we demonstrated error-related impairments of working memory (WM) maintenance by asking subjects to retain information in WM while performing a concurrent motor task (error-related impairment of active working memory, ERIAM). The current study aimed to corroborate and further investigate the ERIAM effect by examining the neural correlates of WM via contra-lateral delay activity (CDA) measured through EEG, and by employing Bayesian hierarchical mixture modeling to provide additional insights into the nature of the behavioral deficit. Subjects (N=42) were instructed to maintain three color items at the cued side in WM while completing a flanker task during the retention period. Subsequently, a WM probe was presented with a color wheel, and subjects were

asked to report the corresponding color on the color wheel. Consistent with our previous findings, subjects showed a behavioral ERIAM effect. Bayesian modeling revealed that this disruption was strongly predicted by a decrease in the probability that responses originated from a target memory representation. Error commission similarly increased probability of responses coming from non-target representation and guesses by 5%. Furthermore, the CDA analysis showed that the CDA changed to significantly more positive deflection following correct responses compared to errors, suggesting that neural representation of WM was affected by error commission. In summary, our findings shed light on the multifaceted nature of WM impairment following error commission, providing both neurophysiological evidence and model estimates of the ERIAM effect.

Disclosures: Y. Choo: None. **K.C. Adam:** None. **J.R. Wessel:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.13/U9

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01MH131559

Title: Decoding composition and generalization of task representations in hierarchical task learning

Authors: *W. LEE[1,2], E. HAZELTINE[2], C. GREENE[2], Q. HONG[2], J. JIANG[2];
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Abstract: Humans have remarkable abilities to learn and perform many tasks in ever-changing life. This ability is in part supported by the hierarchical organization of task representations. For example, the task of making Latte is composed of two simpler tasks of making espresso and steaming milk. Compositions sharing the same simple tasks further facilitate generalization to new compositions. For instance, knowing latte = espresso + milk and hot chocolate = milk + chocolate syrup help form a new task to combine espresso and chocolate to make mocha. Using electroencephalographic (EEG) data (n = 40), we tested the hypothesis that learning a complex task relies on reinstating the simple tasks involved. In the training stage, participants learned six simple tasks (coded as A-F) and then complex tasks consisting of two simple tasks (e.g., AB, BC). In the test staged, subjects performed new complex tasks that can be generalized from learned complex tasks (e.g., AC from AB and BC). We successfully replicated the behavioral generalization effect. In the EEG data, reinstatement was operationalized as decoding encompassed simple tasks from a complex task (e.g., A from AC, termed composition effect) and decoding the unpresented shared simple task (e.g., B from AC, termed generalization effect). Composition effect manifested during the training stage of complex task, while generalization effect became evident during the test stage. This finding was further supported by two

correlations: (1) between behavioral and EEG generalization effects and (2) between EEG composition effect in training stage and EEG generalization effect in test stage.

Disclosures: W. Lee: None. **E. Hazeltine:** None. **C. Greene:** None. **Q. Hong:** None. **J. Jiang:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.14/U10

Topic: H.04. Executive Functions

Support: R01MH131559

Title: Dynamics of multi-form task representations during sequence learning

Authors: *G. YANG, Q. HONG, S. HAN, J. JIANG;
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Abstract: While humans can rapidly learn new tasks, the underlying task representations are less known. We propose that a task can be represented in various formats. For instance, cooking can be represented as a sequence of steps (sequence form), a collection of discrete tasks (task-form), or as interconnected subtasks linked by transitions (transition-form). We further hypothesize that these representations can be formed and altered through learning. To test these hypotheses, we designed a delayed matching paradigm and collected EEG data. On each trial, participants were asked to remember a five-feature compound stimulus and choose from option features to match the stimulus after a delay. Five trials form a sequence, each following a predetermined order of cued features. Effective sequential/transition memory can predict the upcoming cued feature, potentially reduce the demand of working memory load. We tested the dynamics of these representational forms by training participants on one/three/eight sequences within three sessions of equal duration, while different sequences shared varying numbers of feature transitions. Model-free analyses suggested that the sequence learning influenced the demand of working memory load, and the training frequency of transitions influenced the performance. We developed a model with a hidden memory strength variable for each representational form, with their strengths getting updated with learning. This model showed better fitting goodness to behavioral data from 48 participants compared to its deprecated models, supporting the existence of different representation forms and characterized their learning dynamics. We conducted model-based EEG analyses, focusing on both event-related potentials and multivariate decoding (classifying five feature types). We found that a stronger sequence representation decreases the posterior late positive potential amplitude and enhances the decoding accuracy before and after the appearance of the cued task. We also found the feature in trial N+1 is decodable in trial N for sequences with stronger transitions, indicating a representation of transition. Overall, our

findings underscore the dynamic changes of task representations in different forms during task learning.

Disclosures: G. Yang: None. **Q. Hong:** None. **S. Han:** None. **J. Jiang:** None.

Poster

PSTR483: Roles of Memory in Cognitive Flexibility

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR483.15/U11

Topic: H.04. Executive Functions

Support: R01MH131559

Title: Hippocampo-cortical contributions to the structured organization of tasks

Authors: *B. BUSTOS[1], Y.-Y. CHENG[2], C. GREENE[2], Q. HONG[2], J. JIANG[3];
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Abstract: Successful task switching requires resolving the interference from the old task and/or reconfiguring the representation of the new task, both of which rely on how task representations are organized in the brain. On one hand, tasks can be encoded in completely orthogonal representations to minimize interference. However, this would incur maximum reconfiguration at every task switch. Alternatively, it is possible that task knowledge is encoded under a common reference frame, such that interference and reconfiguration costs of task switch are balanced by tuning the similarity between task representations. One candidate for such reference frames is a cognitive map, a ubiquitous organizational structure of various relationships. A cognitive map provides a mental model of relationships between given information. In the context of task representations, task features (e.g., task rules) can be coded as continuous parameters like coordinates on a map, such that each point on the map uniquely identifies a task. We test this prediction using a parametric task-switching paradigm with high spatial resolution 7T fMRI. Here we focus on the role the hippocampus and cortex jointly play in supporting the construction and organization of relational maps of task knowledge such as stimulus, response, and rule representations as these areas provide crucial support for the construction of relational cognitive maps. Leveraging hippocampo-cortical RSA, we expect to observe pattern similarity scale with the similarity between tasks in the frontoparietal cortex, where task information is represented during execution. Furthermore, we expect that the strength of pattern similarity to task similarity correlation in the frontoparietal cortex is linked to hippocampal activation, due to the importance of the hippocampus in supporting a cognitive map. To probe how the fidelity of the cognitive map and strength of the parametric representation influences cognitive flexibility we will examine the relationship between neural measures such as RSA scores and retrieval strength, and behavioral reconfiguration costs. Preliminary data (n = 5) shows a positive correlation between task similarity and brain activity pattern similarity in inferior frontal, frontopolar, and anterior

insular areas across all participants. Understanding the organization of task rules will provide crucial insight into how the memory organization of task knowledge facilitates cognitive flexibility.

Disclosures: B. Bustos: None. **Y. Cheng:** None. **C. Greene:** None. **Q. Hong:** None. **J. Jiang:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.01/U12

Topic: H.05. Working Memory

Support: NIMH Grant U01MH130447

Title: Preliminary quality and reliability of the resting and task fMRI data from the Philadelphia theta burst collection.

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[1]Univ. of Pennsylvania Dept. of Psychiatry, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Psychiatry, Univ. of Pennsylvania Deptartment of Psychiatry, Philadelphia, PA

Abstract: Recent neuromodulation studies have shown convincing evidence that theta burst stimulation (TBS) of the dorsolateral prefrontal cortex (dlPFC) can improve cognitive processes involved with emotion regulation. However, the specific mechanistic changes that occur in the brain remain relatively unexplored. This study aims to determine changes in functional connectivity between the left dlPFC (target site) and its downstream connection using the electric (e)-field distribution to model the changes. We examined changes following two patterns of stimulation: intermittent (iTBS) and continuous (cTBS). We hypothesized that iTBS would increase the functional connectivity between the left dlPFC and downstream regions, while cTBS would decrease connectivity. Our study aims to enroll 200 total participants to complete 3 sessions of either iTBS or cTBS, with functional scans performed about 24 hours after each TMS session. We collected 16 minutes each of high-quality multiband multi-echo task and rest fMRI and used TE-dependent independent components analysis to separate noise components from the BOLD signal. Participants are tasked with a variation of the Sternberg letter memory task while in the scan, for both targeting and functional connectivity data. This presentation will feature a preliminary analysis of the quality and reliability of both the imaging and behavioral data from the first 64 subjects in the project. Preliminary findings of the resting state data show good SNR, low levels of motion, and comparable reliability to 1 hour of resting state data from the human connectome project. Preliminary findings of the task data show reliability in the good range for accuracy and dlPFC BOLD. Across sessions, accuracy increased in the iTBS group about 5%,

but decreased by a comparable amount in the cTBS group. With TBS being increasingly applied therapeutically to treat mental illness, it will be increasingly important to understand how TBS modulates network connectivity and how interactions between specific anatomical features and the spatial distribution of the e-field influence these changes. Once complete, the Philadelphia Theta Burst Collection will be one of the largest openly available collections of task and resting state fMRI following TBS.

Disclosures: M. Patel: None. **M. Patel:** None. **A. Casalvera:** None. **M. Teferi:** None. **N.L. Balderston:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.02/U13

Topic: H.04. Executive Functions

Support: NIMH Grant R61MH120245

Title: Effect of a non-pharmacological insomnia treatment on cognitive functioning and memory in adults with comorbid insomnia and depression

Authors: *M. BABROS[1], A. J. KRAUSE[2], M. AHMADI[2], R. OSORNO[2], A. N. GOLDSTEIN-PIEKARSKI[2];
[1]Psychiatry and Behavioral Sci., Stanford Univ., San Francisco, CA; [2]Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Background: Insomnia and depression are both associated with impairments to memory, attention, and executive function. Furthermore, overall cognitive function has been shown to be diminished when the two conditions are comorbid. Cognitive Behavioral Therapy for Insomnia (CBT-I) is the gold standard treatment for insomnia and has been shown to improve cognitive functioning in older adults with mild cognitive impairment, specifically in the domains of immediate and delayed memory. However, there is no current research on the effect of CBT-I on cognitive functioning in adults with comorbid insomnia and depression. The present secondary analysis of a single-armed mechanistic clinical trial aimed to test whether CBT-I improves cognitive functioning in adults with clinically meaningful insomnia and depressive symptoms.
Methods: Data was available for 47 adults (mean age: 40.3 +/- 10.8, 65.9% female) with comorbid symptoms of insomnia and depression who completed all six sessions of CBT-I and cognitive testing at both baseline and end of treatment. Cognitive function was assessed with the RBANS which consists of 12 subtests that inform index scores of immediate and delayed memory, attention, language, and visuospatial construction. Index scores were constructed using standard (m=100, sd=15) age-normalized data from the RBANS test book. The Immediate Memory index score consists of list learning and story memory subtest scores. Delayed Memory

index consists of list recognition, list recall, story recall, and figure recall subtest scores. Attention index consists of digit span and coding scores. Visuospatial/constructional index consists of figure copy and line orientation scores. Language index consists of picture naming and semantic fluency scores. Pre-treatment to post-treatment changes in RBANS index and subtest scores were evaluated with paired t-tests. A Benjamini-Hochberg correction was applied to correct for multiple comparisons.
Results: There was significant improvement in the immediate ($t = 4.77$, adj $p<.0001$) and delayed ($t = 3.45$, adj $p<.001$) memory index scores pre- to post-CBT-I, and there was a trending improvement in the attention index score ($p = 0.037$, adj alpha = 0.03). However, there were no differences in the language and visuospatial index scores ($p's > 0.05$).
Conclusion: Although these results are limited by the absence of a control condition, the observed improvements in immediate and delayed memory support the effectiveness and utility of CBT-I for improving cognitive functioning in adults with co-occurring insomnia and depression symptoms.

Disclosures: M. Babros: None. **A.J. Krause:** None. **M. Ahmadi:** None. **R. Osorno:** None. **A.N. Goldstein-Piekarski:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.03/U14

Topic: H.04. Executive Functions

Support: College of Wooster Hamburger Endowment

Title: Yoga intervention improves ADHD and cognitive measures in emerging adults with ADHD

Authors: S. FAZAZI, *A. STAVNEZER, S. LYNN;
Col. of Wooster, Wooster, OH

Abstract: Attention Deficit/Hyperactivity Disorder (ADHD), impacting ~2.5% of adults, is a chronic neurodevelopmental condition that is characterized by elevated levels of inattention, hyperactivity, and impulsivity. Adult ADHD often presents with disruptions to social life and work, as well as impairments in executive function. Adults with ADHD have exhibited relationships between the cortisol awakening response and IL-6 levels and exhibit significant alterations in cortisol reactivity to stress.
The negative side-effects of pharmaceutical treatment leads to an increasing need to focus on non-pharmaceutical approaches such as cognitive-behavioral therapies, exercise, mindfulness, and meditation interventions. Yoga has been shown to enhance mood, memory, and emotional regulation (Basso et al. 2019), reduce circulating cortisol and IL-6 levels (Riley & Park 2015), and improve attention and processing speed (Gothe & McAuley, 2015) in adults not diagnosed

with ADHD. A recent meta-analysis suggests that yoga practice, which includes a physical exercise component, breathing practices, relaxation, and mindfulness-based meditation, may be an effective form of intervention for children and adolescents with ADHD (Chimiklis et al. 2018), yet studies investigating the effectiveness of yoga on adult ADHD symptoms are mixed (Friz & O'Connor 2022, Dinu et al. 2023), and little is known of the effects of yoga in emerging adults.
To address these gaps, we investigated the effectiveness of an 8-week yoga intervention on cognitive measures (continuous performance task, N-back, Stroop), affective and attention self-report scales (ADHD, daily function, interoception, affect, sleep, stress, mindfulness), physiological markers (waking cortisol, IL-6), and sleep in emerging adults with ADHD. A total of 41 college students with ADD/ADHD participated. Twenty-two received an 8-week yoga intervention with a 500-hour certified instructor, 19 did not.
Preliminary, within-in subjects analysis found benefits of the yoga intervention. Participants in the yoga intervention group decreased their self-reported ADHD measures on the ASRS-v1.1 by more than two standard deviations, $z=3.76$, $p<0.001$, increased their interoception levels on six of the eight MAIA scales, $z=2.16$, $p<0.03$, and improved on number correct in the 2-back task, $t=2.43$, $p<0.03$, over the 8-week time frame. An interpretation of these measures, physiological data and comparisons to the control condition will be discussed.

Disclosures: S. Fazazi: None. **A. Stavnezer:** None. **S. Lynn:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.04/U15

Topic: H.04. Executive Functions

Support: CAPES
CNPQ
FAPERJ
UFF
PROPPI

Title: Participation of the endocannabinoid system in locomotion and risk behavior in an animal model of Attention-Deficit/Hyperactivity Disorder

Authors: *D. B. S. PENNA[1], S. G. COSTA[1], J. SANTOS ROMÃO[1], K. C. CALAZA[2], K. D. OLIVEIRA[3], A. S. DOS SANTOS-RODRIGUES[4], P. PANDOLFO[5];
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Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) affects individuals of all ages and is related to a dopaminergic hypofunction. The endocannabinoids (EC) system is essential in modulating dopaminergic transmission. We investigated the effects of manipulating EC receptors (CB1R and CB2R) on locomotion and risky behaviors ADHD-related and density/gene expression of EC receptors and enzymes during adolescence and adulthood. Male (M) and Female (F) SHR and WKY rats were treated (ip) with WIN (0.25 mg/kg), AM251 (1mg/kg), and AM630 (3mg/kg) or vehicle (1 mL/kg). After 20 min, their locomotion and risk behavior were evaluated in the Open Field test (OF) and Elevated Plus Maze (EPM).The brain frontal cortices were dissected to investigate CB1R, CB2R, FAAH, MAGL protein densities and gene expression using western blot (WB) and qPCR analysis. CEUA nº7626281021. Adolescence - WIN increased locomotion in SHR (OF: 28±1.2mx32±1.3m; EPM: 7±0.2x11±0.2). WIN reduced stretch to attempt posture (SA) in WKY (12±0.6 x 9±0.6). qPCR demonstrated augment of *Cnr1* (1±0.3 x 1.2±0.4), *Cnr2* (1±0.0x1.3±1.1), *Faah* (1±0.0x1.2±0.4) *and Mgll* (1±0.0x1.2±0.7) expression in SHR M. SHR Fexhibit increased *Faah* (1±0.2x1.5±0.4). Adulthood AM251 increased risk behavior in SHR M (OF: 5±0.3mx5.7±0.3m). EPM: AM251 and AM630 treatments increased locomotion in WKY M (4±0.6x7±0.7; 4±0.6x7±0.6, respectively). AM251 treatment reduced risk behavior in WKY M (EPM: 39±5x13±6). AM251 and AM630 treatments increased % time spent in the central platform in WKY M (24±2x36±2; 24±2x39±2); AM251 reduced the number of SA in SHR (9±0.8x6±0.7); WIN and AM251 treatments reduced number of head dipping in SHR (8±0.4x6±0.5; 8±0.4x6±0.4). SHR exhibits increased MAGL density (0.7±0.0x1.1±0.1). SHR F exhibit increased FAAH density WKY (1.0±0.0x1.2±0.1). SHR exhibit increased *Mgll* gene expression in both sexes (M: 1±0.2x1.6±0.1; F: 1±0.2x1.7±0.2) and SHR M increased *Cnr2* (1±0.2x2.5±1.4). In adolescence, hyperactivity is potentiated by the activation of CB1R and CB2R, while in adulthood, CB1R antagonism reduces risk-taking behavior in the ADHD animal model. SHR higher levels of MAGL and FAAH proteins indicate a molecular basis for EC participation in adult ADHD. Different gene expressions indicate an important sex and age influence in the EC system. Activating CB1R and CB2R during adolescence can increase hyperactivity. However, in adulthood, CB1R antagonism can increased risk-taking behavior in the ADHD model. Higher levels of MAGL and FAAH proteins can be involved in adult ADHD. Variations in gene expression suggest that age and sex play an essential role in the endocannabinoid system.

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Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Program #/Poster #: PSTR484.05/U16

Topic: H.04. Executive Functions

Support: National Institute of Mental Health of the National Institutes of Health (NIMH-NIH), R01MH120168

Title: A naturalistic assessment of reaction time and impulsivity throughout the day in those with mood disorders

Authors: *T. M. NGUYEN[1], M. K. ROSS[2], E. NING[2], S. A. LANGENECKER[3], J. DUFFECY[4], J. ZULUETA[5], A. P. DEMOS[5], O. A. AJILORE[6], A. D. LEOW[2];
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Abstract: For patients with psychiatric disorders, impulsivity can lead to disruptive, costly, and potentially harmful outcomes. Although numerous studies have investigated the effects of impulsivity within specific psychiatric disorders, few studies have examined the diurnal patterns of impulsivity in those with psychiatric disorders (i.e., fluctuations throughout the day). Measures such as reaction time variability and time-of-day may better reflect intraindividual patterns and adaptations of impulsivity and fluctuations in cognitive processes. The purpose of this study was to examine the utility of a novel go/no-go task involving a shake response on a smartphone that was completed in-the-wild and determine its ability to detect changes in reaction time and impulsivity based on the time of the day in those with these disorders. To this end, participants with and without a mood disorder (healthy control = 17, 52.9% female; mood disorder = 43, 76.7% female) were recruited as part of the UnMASCK study (ClinicalTrials.gov Identifier: NCT04358900). Participants were categorized in the mood disorder group if they met the DSM-5 criteria for bipolar disorder type I/II, major depressive disorder, persistent depressive disorder, or cyclothymia as determined by a study clinician. We found that hour of the day had a significant quadratic effect on the accuracy of no-go trials and reaction time. Participants tended to respond more accurately in the mornings and evenings compared to the afternoon on no-go trials. Additionally, participants had faster reaction times in the afternoon compared to the mornings and evenings. Depression severity had a significant linear effect on reaction time in that those who were more depressed as determined by their baseline QIDS score had slower reaction times compared to those less depressed. There was also a significant difference in reaction time based on the trial type; incorrect no-go trials had faster reaction times than correct go trials. This trend was consistent throughout the hours of the day. Lastly, a practice effect was observed in no-go trials with improved trial accuracy following more completed GNG tasks; this effect, however, did not impact reaction time. We propose a novel go/no-go task capable of being completed repeatedly in a naturalistic setting. This task is sensitive to the influence of time of day and depression severity on reaction time and impulsivity. Since cognitive performance is impacted by mood disorder symptoms, our GNG task could serve to monitor aspects of cognition over time without increasing the time burden on these individuals.

Disclosures: T.M. Nguyen: None. **M.K. Ross:** None. **E. Ning:** None. **S.A. Langenecker:** None. **J. Duffecy:** None. **J. Zulueta:** None. **A.P. Demos:** None. **O.A. Ajilore:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); cofounder of KeyWise AI. F. Consulting Fees (e.g., advisory boards); advisory board of Embodied Labs and Blueprint Health. **A.D. Leow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); cofounder of KeyWise AI. F. Consulting Fees (e.g., advisory boards); medical advisory board for digital medicine for Otsuka.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.06/U17

Topic: H.04. Executive Functions

Support: NIMH R01MH119164
NIMH R01MH118332
NIMH R01 MH130825

Title: Postnatal Enrichment Normalizes Deficits in Reversal Learning and GABAergic Innervation in the Orbitofrontal Cortex of Adult Mice Exposed to Early Adversity

Authors: *A. KAFFMAN[1,2], R. ISLAM[3], S. AHMED[4], C. BOWERS[3], L. GIULIANO[3], S. JAMWAL[4];
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Abstract: Childhood neglect accounts for 60% of all early life adversities and is associated with profound cortical thinning, hyperactivity, and cognitive deficits, including abnormal reversal learning. The molecular and cellular mechanisms responsible for these neurodevelopmental changes are difficult to study in humans, and no animal models have yet replicated key structural and behavioral features of early deprivation/neglect. We have recently shown that mice exposed to impoverished conditions, in the form of limited bedding (LB) exhibit behavioral and structural changes that resemble those seen in children and adolescents exposed to early neglect. Here, we investigated the impact of LB on reversal learning in adult mice and whether early enrichment from postnatal day 14 (P14) to P25 can reverse these deficits. Indeed, using the Barnes maze reversal learning paradigm, we found that LB caused severe deficits in reversal learning in adult male and female mice. These deficits were fully reversed through early enrichment. LB mice exhibited reduced c-fos activation in the orbitofrontal cortex (OFC) during reversal learning, which was linked to a decrease in the number of parvalbumin (PV)-positive cells, reduced GABAergic synapse density, and an increase in the density of glutamatergic synapses in the OFC. These effects were all reversed by early enrichment. The number of PV-positive cells surrounded by perineural nets (PV+PNN+) was reduced in the OFC of LB mice and normalized in LBT mice. Finally, the degradation of PNN in the OFC of control mice resulted in deficits in reversal learning, c-fos activation, and reduced GABAergic synapse innervation that resemble outcomes observed in LB mice. These findings suggest that abnormal GABAergic innervation in the OFC is responsible for the long-term deficits in reversal learning observed in a mouse model of early neglect and that postnatal enrichment can reverse the synaptic and cognitive abnormalities observed in LB mice.

Disclosures: A. Kaffman: None. **R. Islam:** None. **S. Ahmed:** None. **C. Bowers:** None. **L. Giuliano:** None. **S. Jamwal:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.07/U18

Topic: H.04. Executive Functions

Support: NHMRC/MRFF Investigator Grant #1193946

Title: Empirically examining the potential bidirectional role of cognitive inflexibility and eating disorder symptoms

Authors: T. COPELAND, ***R. LEE**;
Univ. of Melbourne, Melbourne, Australia

Abstract: Neurocognitive dysfunction, including cognitive inflexibility, has long been implicated in eating disorders. Clinical research, however, has yet to definitively establish whether it is a risk factor for, or outcome of, disordered eating. Here, we sought to statistically model the role of cognitive inflexibility across different clinical phenotypes in a general community sample reporting eating disorder symptoms. We hypothesised that cognitive inflexibility and eating disorder symptoms would be bidirectional; namely, they would be predictive of each other while adjusting for known confounds. A mixed community sample was recruited, consisting of 195 people aged 17 to 34 (mean age = 20.6 years; 150 female). Participants completed an online survey measuring self-reported symptoms of disordered eating, depression, and performance on a set-shifting task (Wisconsin Card Sorting Test). Analyses revealed that failure to maintain set was positively associated with global disordered eating, restrictive eating, and binge eating behaviours. After controlling for age, body mass index, and depressive symptoms, failure to maintain set significantly predicted restrictive (β=0.167, p=.03) and binge eating behaviours (β=0.971, p=.001). Conversely, binge eating also predicted failure to maintain set (β=0.056, p=.001), revealing a bidirectional relationship for this specific clinical phenotype. Set-maintenance may be an early risk factor for disordered eating behaviours, as well as an outcome of binge eating. This suggests cognitive inflexibility may be a potential neurocognitive target for early intervention. Alternatively, working memory may be construed as a contributor to eating disorder symptoms since it is also implicated in failure to maintain set difficulties and warrants further clarification. The temporal mechanics of neurocognition and eating disorders require longitudinal investigation.

Disclosures: T. Copeland: None. **R. Lee:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.08/U19

Topic: H.04. Executive Functions

Title: Possible correlation between HIV genotype and cognitive impairments in a shelter patients of Tijuana Mexico

Authors: *L. AZUARA ALVAREZ;
Univ. Autónoma de Baja California, Tecate, Mexico

Abstract: L. E. AZUARA ALVAREZ[1,3], N. A. CASTILLO MARTINEZ[2], M. L. GARCIA GOMAR, A.NEGRETE CORTEZ1, J. R. CHAVEZ MENDEZ[3]1 Universidad Autónoma de Baja California, México,Unidad Valle de las palmas,biochemistry laboratory2 UABC,UVDP, microbiology laboratory3 UABC,UVDP, infectology and genomic laboratoryIt is known that HIV can generate important cognitive affections due to its tropism throughthe central nervous system generating a process called HIV-Associated NeurocognitiveDisorder (HAND). Las Memorias Shelter in Tijuana Mexico (ALMAC) is a place where about150 patients with HIV, tuberculosis, addictions, migrants, homelessness and LGBTQ+. 130of which are HIV positive. One of ALMAC's objectives has been to create programs thatallow reinsertion into society, such as the creation of a technical nursing school within theshelter, or the management of academic scholarships for those who decide to finish theirbasic and university studies. Due to the high incidence of HIV in our population and the factthat patients report or manifest cognitive alterations, which makes it difficult for our patientsto achieve reintegration into society, we were interested in performing genotype analysis andevaluating if there is any relationship with the alterations in cognitive tests. Of 122 patientswho were allowed to be evaluated, 48 samples were amplified with the complete HIVgenome, then sequenced using the Sanger method and aligned with MEGA program. Inparallel, 13 tests were performed to evaluate cognitive alterations and the following wasfound. 20 of our patients who share HIV genotype present alterations in MoCA, whichevaluates the following parameters: memory, visuospatial capacity, executive function,attention and working memory. This is quite significant for our population because one of thegoals of our shelter is to reintegrate them into society and to help them obtain a trade oracademic preparation, which could explain why this important step in their stay at ALMAC isso complicated for our population. 11 of our patients have alterations in tests that measureimpulsivity, which could explain why some of our patients frequently relapse in the use ofsubstances and suspend the activities of reinsertion into society that the shelter provides.Part of the current strategies to solve this problem has been the modification of the teachingmethodology for those who are attending the technical school of nursing and the creation ofstudy groups with those who are attending basic or university preparation in search ofimproving academic performance. We are still evaluating these results.

Disclosures: L. Azuara Alvarez: None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.09/Web Only

Topic: H.04. Executive Functions

Support: University of Guanajuato 099 2024

Title: Executive functions are correlated with body mass index in overweight middle aged women

Authors: *M. SOLIS-ORTIZ;
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Abstract: Excess body weight is currently recognized as one of the most serious public health problems in the world, given its magnitude, rapid growth, and its adverse effect because it significantly increases the risk of chronic degenerative diseases. The impacts of excess Body Mass Index (BMI) on physical health are well known and widely studied, but little is known about the consequences of being overweight or obese on cognitive function. The aim of this study was to correlate the BMI with executive functions in overweight middle aged women. Seventy overweight middle aged women between 48 and 64 years of age who are otherwise healthy participated in the study. Demographic and anthropometric variables were evaluated. Four standard neuropsychological tests were applied to assess executive functions, sustained attention, selective attention, and verbal fluency. The mean BMI of the participants was 29.35 and was negatively correlated with categories reached and positively correlated with the number of errors of executive function test. Scores of other neuropsychological tests applied showed no correlation with BMI. These findings suggest that BMI impacts the executive functions in overweight women who do not present any signs of disease. Therefore, we must pay attention to diet and exercise for weight loss and its impact on cognition.

Disclosures: M. Solis-Ortiz: None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

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Program #/Poster #: PSTR484.10/Web Only

Topic: H.04. Executive Functions

Support: DGAPA UNAM IN232120
UNAM DGAPA Postdoctoral Scholarship for I. O. Conde-Rojas

Title: Exploring the Associations of Food Addiction with Executive Functioning, Depression, and Reinforcement Sensitivity in Mexican Adults

Authors: *R. ESCARTIN-PEREZ[1], J. O. SUAREZ-ORTIZ[2], F. CORTÉS SALAZAR[1], I. O. CONDE ROJAS[1], V. LÓPEZ-ALONSO[1], J. MANCILLA-DIAZ[1];

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Abstract: Food addiction (FA) as a clinically identifiable pathological condition has gained recognition due to advances in the study of the neurobiological factors underlying the symptomatology of food dependence. The changes in brain functioning resulting from chronic consumption of hyper-processed palatable foods are qualitatively similar to the effects of known substances of abuse, which has enabled a better characterization of the abnormal eating patterns that contribute to excessive weight gain. As a result, the relationship between FA traits and impaired executive functioning in overweight or obese individuals has been investigated in terms of the similarity between compulsive food consumption patterns and addictive behaviors. Consequently, researchers have suggested the existence of a cognitive profile that is comparable to that of substance addiction but directed toward palatable foods. Accordingly, this study aimed to ascertain whether the presence of executive dysfunction (ExDys), depressive symptoms (DSymp), binge eating traits (BET), and elevated reward sensitivity (RSen) correlate with increased severity of FA symptoms and higher body mass index (BMI) among a sample of Mexican adults. Our sample comprised Mexican adults aged 21 to 59 (n=36), who completed self-reported questionnaires and performance tests measuring FA, ExDys, DSymp, BET, and RSen. BMI was estimated using self-reported height and weight. Our findings revealed that the number of FA symptoms correlated positively with elevated scores of ExDys, heightened RSen, and more severe depressive and binge eating issues. Notably, severe ExDys, increased activation of the punishment avoidance system, and persistence in seeking reward were strongly associated with higher FA scores, particularly in the presence of severe DSymp. Among women, decreased crystallized intellectual capacity and loss of control over food intake were primary factors linked to changes in BMI as FA symptoms intensified. In synthesis, a cognitive profile marked by overall executive functioning failure, coupled with heightened punishment avoidance system activation, and persistence in seeking reward, was associated with greater FA severity, especially when the DSymp was severe. Concurrently, the psychopathology observed in participants with FA underscored the influence of anxious and depressive symptoms, as well as borderline personality traits, which could facilitate the manifestation of clinically significant FA symptoms in women. Lastly, diminished crystallized intellectual capacity and impaired food intake control were found to correlate with higher BMI as FA symptoms escalated.

Disclosures: R. Escartin-Perez: None. **J.O. Suarez-Ortiz:** None. **F. Cortés Salazar:** None. **I.O. Conde Rojas:** None. **V. López-Alonso:** None. **J. Mancilla-Diaz:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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The Kiwanis Foundation

Title: Exploring the influence of handedness in the localization of general cognitive ability

Authors: *B. MCNICHOL[1], M. BOWREN, Jr.[2,3,4], K. LANGBEHN[2], J. D. SKYE[5,6], A. D. BOES[2,7,3], D. TRANEL[2,6];
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Abstract: The optimal neuromodulation targets for treating cognitive dysfunction may differ systematically across individuals based on key patient attributes. In our previous work, we demonstrated that general cognitive ability (g) depends on integrity of the left hemisphere white matter. Though it has been established that left-handed individuals may differ in brain organization for language lateralization, it is unclear whether the critical neural correlates of g are different among individuals who are left- or mixed-handed. Here, we used lesion-symptom mapping to elucidate brain regions critical for general cognitive ability (g) in patients with focal brain damage who are left- or mixed-handed. Data were derived from the Iowa Neurological Patient Lesion Registry. The sample included 40 patients with focal brain lesions (21 men; 39 White; mean years of education = 13.98, SD = 2.76; average age at lesion onset of 55.2 years, SD=12.44) who were left- or mixed-handed. We measured handedness using the Edinburgh Handedness Inventory, and we deemed patients to be mixed- or left-handed if they had a score of 40 or less. Patients completed at least 75% of a diverse battery of cognitive and neuropsychological measures previously used to study general cognitive ability (g) and did not have a developmental lesion etiology (stroke *n*=33, encephalitis *n*=1, head trauma *n*=1, resection *n*=5). MRIs or CTs were used to delineate lesion masks (i.e., the voxels with a lesion present). Lesion masks were co-registered to the MNI152 1mm template. We identified brain regions associated with lower g using a multivariate lesion-symptom mapping technique based on sparse canonical correlation analysis (SCCAN). The lesion-deficit map was used to predict g scores and compared against observed g scores. Although the lesion-symptom map was not statistically significant (Pearson correlation between observed and predicted g = 0.234, p = .146), voxel values suggested that lower g scores were associated with damage to the left posterior white matter deep to the temporoparietal junction, the left anterior white matter deep to the posterior lateral prefrontal cortex, and the right sub-insular white matter and claustrum. Although limited by a small sample size, our findings suggest that the neural correlates of g in non-right-handed individuals do not differ from those of the general population. This suggests that lesion maps derived from right-handed individuals may be applied equally well for general cognitive function regardless of patient handedness. These findings may be informative for future neuromodulation targets.

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Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.12/U21

Topic: H.04. Executive Functions

Support: NIA/NINDS R01NS100849-05

Title: Longitudinal Alterations in Functional Connectivity and Cognition in Parkinson's Disease

Authors: *H. TWEDT[1], B. E. YEAGER[1], N. S. NARAYANAN[2];
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Abstract: Longitudinal Alterations in Functional Connectivity and Cognition in Parkinson's Disease
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Disclosures: **H. Twedt:** None. **B. Yeager:** None. **J. Schultz:** None. **N. Narayanan:** None.
Abstract: Changes to functional connectivity have been evidenced in Parkinson's disease (PD), but the effects that lead to cognitive dysfunction and how connectivity changes over time have yet to be fully elucidated. We investigated the specific alterations in the brain's functional architecture over time, with a focus on three canonical cortical networks (salience network(SN), frontoparietal network (FPN), and default mode network (DMN)) and the subcortical basal ganglia network (BGN). These networks largely contribute to normal cognition, and previous work has shown major changes in network functionality with both aging and disease processes. We hypothesize that functional connectivity both within and between networks will change over time in PD patients and relate to cognition. Neuroimaging data were used from the Parkinson's Progression Marker Initiative (PPMI) dataset (N = 102). FMRI data were processed and analyzed using the CONN toolbox in MATLAB, where ROI-to-ROI and seed-to-voxel measures were computed for network connectivity, and then Pearson's correlation coefficients were Fisher r-to-z transformed. We compared functional connectivity strength between three groups: healthy controls (n = 20), PD patients with normal cognition (PD-Norm; n = 67), and PD patients with mild cognitive impairment (PD-MCI; n = 15). A linear mixed effects model was used to evaluate the effect of group on functional connectivity. Our models compared differences in Montreal Cognitive Assessment (MoCA) scores to changes in functional connectivity in PD patients from FMRI scans at their initial visit compared to their second and third visit. Significant relationships were noted between MoCA changes and changes in intra-FPN connectivity and inter- DMN-FPN, DMN-SN, and SN-BGN connectivity. These data provide evidence that functional connectivity may be used as a predictor of future cognitive decline in PD patients.

Disclosures: H. Twedt: None. **B.E. Yeager:** None. **N.S. Narayanan:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.13/U22

Topic: H.04. Executive Functions

Support: NIH 5R01NS100849-05

Title: Sex differences in neural dynamics underlying cognitive impairments in Parkinson's disease

Authors: *B. E. YEAGER[1], H. P. TWEDT[1], A. SINGH[2], J. E. BRUSS[1], J. SCHULTZ[3], R. C. COLE[4], N. S. NARAYANAN[1];
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Abstract: Male sex is a significant risk factor for Parkinson's disease (PD) as men have twice the likelihood of being diagnosed with PD. Additionally, being male is a significant predictor of transitioning to a cognitively impaired or demented patient status. Despite the marked sex differences in PD epidemiology and symptomology, the neural dynamics underlying cognitive impairment in PD have not been extensively analyzed between sexes. We analyze sex differences in PD in two ways. First, we analyzed resting state functional magnetic resonance imaging (rs-fMRI) and neuropsychological assessment data of 82 patients with PD (25 women) from the Parkinson's Progression Markers Initiative dataset. We assessed cognition with the Montreal Cognitive Assessment (MoCA) and found that men had significantly worse global cognition than women. Additionally, weaker salience network-basal ganglia network connectivity predicted worse cognition in men but not women. Second, we analyzed electroencephalography (EEG) data during a Simon reaction-time task; our prior work demonstrated significantly attenuated midfrontal low-frequency cue-evoked power in PD compared to healthy adults. In 122 PD patients (38 women), we found that men performed with less accuracy on the Simon task than women but there were no differences in reaction times. Wavelet-based time-frequency analysis revealed that men had significantly lower midfrontal low-frequency delta (1-4 Hz) and theta (4-8 Hz) power than women for both congruent and incongruent trials. We also found that low-frequency power during incongruent trials in the Simon task predicted worse global cognition in men but not women. This study shows sex differences in PD network dynamics and may inspire novel biomarkers that are more precise and individualized to patients which may improve diagnosis and treatment of PD.

Disclosures: B.E. Yeager: None. **H.P. Twedt:** None. **A. Singh:** None. **J.E. Bruss:** None. **J. Schultz:** None. **R.C. Cole:** None. **N.S. Narayanan:** None.

Poster

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Topic: H.04. Executive Functions

Support: University of Rochester Intellectual and Developmental Disabilities Research Center (IDDRC, P50HD103536)
The Schindler Foundation

Title: Cognitive-motor interactions in those with and without Autism Spectrum Disorder using mobile brain-body imaging, MoBI, show differences in neurophysiology and response inhibition task performance

Authors: *P. R. NICKLAS[1], E. G. FREEDMAN[2], J. J. FOXE[2];
[2]Del Monte Inst. for Neurosci., [1]Univ. of Rochester, Rochester, NY

Abstract: Cognitive-motor (C-M) interference occurs when the demands of concurrent cognitive and motor tasks compete for the available neural resources, potentially leading to performance decrements in one or both tasks. Research commonly investigates this phenomenon by employing dual-task designs to compare performance under single-task to dual-task conditions, which require both motor and cognitive engagement. However, recent findings challenge the concept of C-M interference, as approximately half of a cohort of young adults (YAs) demonstrated improvement on a response inhibition (RI) task while walking. Those who showed improvement exhibited significant differences in neurophysiological and gait profiles compared to non-improvers. This suggests that while some individuals do experience C-M interference, others demonstrate a more integrated response, adapting better to multi-modal demands. Yet, the factors that determine an individual's directionality of C-M interactions and their developmental trajectory remains unclear. Previous work suggests inhibition becomes more focused with age, shown through improved performances, and more frontal and concentrated distributions of neural topographies, but its dual-task dynamics remain unexplored. Further, one of the most common developmental disabilities, Autism Spectrum Disorder (ASD), is under-explored from dual-task perspectives despite known motor, cognitive, and sensory differences in individuals within this population. Specifically, how different deficits in these single-modal domains interact in multi-modal contexts during development warrants investigation. To address these questions, we utilize Mobile Brain-Body Imaging (MoBI), enabling simultaneous recording of neurophysiological (electroencephalography/EEG), kinematic (motion-tracking), and behavioral (task performance) data. Notably, this is the first study to use these methods in individuals under 18 years old. Participants aged 8-30 years engage in a Go/NoGo RI task while seated and walking on a treadmill, and data collection includes cognitive assessments, physical activity surveys, and biometric measurements. Preliminary results show motion-state related differences within each group in gait variability, task performance, but only in the neurotypical group for ERP amplitudes. Currently, individual factors are not significantly correlated with the change in ERP amplitudes, gait, or task performance from sitting to walking in either group, suggesting

that the dual-task C-M interactions are not due to any single-modal ability or measurement. Data collection is ongoing to properly power all analyses.

Disclosures: P.R. Nicklas: None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.15/U24

Topic: H.04. Executive Functions

Support: FRAXA Research Foundation

Title: Examining the puzzle box test as a behavioral assay for cognitive flexibility in Fragile X syndrome

Authors: *P. S. PIRBHOY[1], O. STEWARD[2];
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Abstract: Fragile X syndrome (FXS) is caused by the expansion and hypermethylation of the CGG trinucleotide repeats in the 5'-untranslated region of the fragile X messenger ribonucleoprotein 1 (*fmr1*) gene, resulting in transcriptional silencing and loss of the *fmr1* gene product. FXS is the leading known cause of intellectual disability. An underexplored aspect of cognitive impairment is cognitive flexibility, or the ability to adapt behaviors in response to changes in the environment. Researchers implement behavioral paradigms assessing reversal learning or extinction paradigms to assess cognitive flexibility in preclinical rodent models. These tasks involve substantial training and experimenter effort, often yielding inconsistent results. Thus, this study aimed to validate the use of the Puzzle Box test to assess cognitive flexibility in FXS. The Puzzle Box is a two-chambered apparatus with a brightly illuminated area and an enclosed goal area. Obstacles of increasing difficulty block the doorway and underpass between the chambers, encouraging mice to acquire a new strategy to reach the goal area. The time to reach the goal area is measured, and a maximum time of 300 seconds is recorded if a mouse does not enter the goal area. To assess cognitive flexibility, male and female *fmr1* knock-out (KO) vs. wildtype (WT) littermate mice postnatal day 80 were tested in three trials per day over three days. Males and females were tested in separate sessions. Results show that both *fmr1* KO (N=27) and WT (N=25) male mice display a significant increase in time to goal from trial 2 (T2) to T5, as the difficulty of the obstacle presented increased. Unexpectedly, WT male mice displayed increased time to goal during T1 compared to *fmr1* KO mice. In contrast, there was a significant genotype difference between *fmr1* KO (N=26) vs. WT (N=18) female mice during T5 and T8, when novel problems were presented. Here, female *fmr1* KO mice displayed increased time to goal compared to WT female controls. Both female *fmr1* KO and WT mice also displayed increased time to goal from T2 to T5 as the obstacle's difficulty increased. When

comparing female vs. male *fmr1* KO mice, both display increased time to goal from T2 to T5. When comparing bedding trials 5-7, females exhibit decreased time to goal, but when comparing plug trials 8-9, females exhibit significantly increased time to goal. These results reveal that female *fmr1* KO mice exhibit cognitive flexibility deficits compared to female WT controls. Results also suggest that *fmr1* KO males and females may excel selectively in specific tasks. Overall, the Puzzle Box test may serve as a potential rapid screening test for cognitive flexibility impairments in FXS rodent models.

Disclosures: P.S. Pirbhoy: None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder, scientific advisor, and has economic interests in the company Axonis Inc, which is developing novel therapies for spinal cord injury and other neurological disorders.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.16/U25

Topic: H.10. Human Learning and Cognition

Support: WorkSafe BC
Mitacs Accelerate Fellowship

Title: Electrophysiological signatures of performance monitoring in functional cognitive disorder

Authors: *J. GUO[1], N. D. SILVERBERG[2], R. M. TODD[2], A. T. HERDMAN[3];
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Abstract: Functional cognitive disorder (FCD) refers to distressing and disabling cognitive symptoms that cannot be explained by neurological diseases or structural changes in the brain. Patients with FCD often present a discrepancy between objectively measurable and subjectively reported cognitive symptoms. The pathophysiology of FCD is not well understood. One proposed mechanism is poor metacognition, where individuals engage in heightened self-monitoring (causing them to notice more cognitive lapses) and negatively biased self-evaluation (interpreting their lapses as frequent, abnormal, and problematic). In our study, we recruited participants with (n=37) and without (n=27) persistent memory symptoms (>6 months) after a mild traumatic brain injury, an exemplary precipitant of FCD. We used electroencephalogram (EEG) to measure brain activity while participants completed a recognition memory task. We hypothesized that in comparison to controls (who reported recovering well after concussion), participants with FCD after concussion would have similar recognition memory accuracy but stronger event-related potential (ERP) amplitudes that reflect heightened performance

monitoring. Our preliminary results showed diminished activity in the FCD group when low-confidence responses were made compared to high-confidence responses at channel Pz, whereas no such effect was observed in the control group. A later differentiation of ERP amplitudes by level of confidence at the same channel between 250ms-500ms was observed only in the control group, which suggests that participants with FCD were evaluating confidence before or during the act of responding, whereas the control participants evaluated their confidence levels after they responded. The FCD group also showed less sensitivity to feedback valence observed around 200ms and 400ms after feedback onset at channel Fz. This study is the first electrophysiological investigation of FCD, and our results identified potential neural signatures of performance monitoring and evaluation that contribute to our understanding of the cognitive mechanisms underlying FCD.

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Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.17/U26

Topic: H.04. Executive Functions

Support: NIH R21#1R21MH127009-01A

Title: Role of frontotemporal networks in anxiety and depression during the performance of a cognitive control task

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Abstract: Neuropsychiatric disorders are the foremost cause of disability in the United States, and targeting brain circuitry underlying functional deficits may yield robust therapeutic strategies. Cognitive control is often compromised in anxious and/or depressed individuals and can be estimated with an interference task where subjects suppress a natural response to overcome response conflict. Conflict evokes robust electrophysiologic signatures in prefrontal cortex (PFC), and recent data suggests lateral temporal lobe (LTL) involvement during conflict. However, it is unclear how anxiety/depression modulates such circuits/rhythms, and the role of LTL in executive function is not well-characterized. The objective of this work is to determine the role of frontotemporal structures modulating cognitive control and identify aberrant neural signatures of cognitive control in individuals with anxiety/depression.
Intracranial EEGs were recorded in frontotemporal regions of 28 human subjects with intractable epilepsy while performing a multi-source interference task (MSIT). Subjects were labeled as

controls or anxious/depressed following neuropsychological evaluation. Spectral parameterization was performed to extract oscillatory peaks in low frequency (4-15Hz), and beta (15-30Hz) bands. Power and coherence in were estimated in spectral peaks and across gamma (30-55Hz) and high-gamma (70-110Hz). For each frequency band and brain region, we fit a generalized linear mixed-effects model (GLME) of power or coherence as a function of Conflict (Low, High) and Group (Control, Anxious/Depressed).
In anxious/depressed subjects, conflict increased low frequency power and reduced beta power in PFC, whereas it increased PFC and orbitofrontal beta and high gamma power in controls. Conflict evoked wideband LTL oscillations in both groups, but to a greater extent in anxious/depressed individuals. Additionally, anxious/depressed subjects had wideband reductions in PFC-LTL coherence and increased low frequency PFC-amygdala coherence during greater cognitive load, whereas conflict increased low frequency PFC-LTL and anterior cingulate-hippocampal coherence in control subjects.
Cognitive control deficits in anxiety/depression may be characterized by dysregulated oscillatory activity. We found that individuals with anxiety/depression demonstrate frontotemporal differences in conflict encoding and functional connectivity during greater cognitive load. Further analysis of neural dynamics in anxious/depressed individuals during cognitive control may aid in identifying potential therapeutic targets for psychiatric brain stimulation.

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Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Program #/Poster #: PSTR484.18/U27

Topic: H.04. Executive Functions

Support: Doctoral Fellowship in Indraprastha Institute of Information Technology, Delhi, India

Title: Mapping fear affect and inhibition: Insights from resting state functional connectivity

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Abstract: Fear affect, a component of the emotional aspect of the National Institutes of Health (NIH) toolbox for the Assessment of Neurological and Behavioral Function, mainly indexes the cognitive component of anxiety stemming from perceived threats and reports on its resting-state functional connectivity (rsfc) correlates, specifically in young adults are sparse to date. Since anxiety is known to impact higher cognitive functions in daily life, potentially leading to cognitive-behavioral disorders, we aimed to identify salient whole-brain rsfc patterns that explain

the negative affect associated with it and the role it plays in influencing the rsfc patterns related to an aspect of executive function (inhibitory control on visual distractors) in 400 healthy, young adults (age = 22-36 years; 199 females). Utilizing the Human Connectome Project dataset, we conducted exploratory, whole-brain multiple regression analyses with parcel-to-parcel rsfc as the independent and fear affect indices of individuals as the dependent variable after controlling for age, gender, and zygosity. This yielded a positive correlation of 13 pairwise connections of parcels (with)in the a) visual and cingulo-opercular network, b) frontoparietal network, c) cingulo-opercular and the default mode network, d) ventral attention and dorsal attention network, and e) default mode network (all *ps* < 0.0059; Family Wise Error (FWE)-corrected). Next, a significant interaction between the fear affect indices and pairwise rsfc of parcels, towards explaining the executive inhibitory control indices was evident after controlling for the earlier nuisance covariates (all *ps* < 0.035; FWE), suggesting a significant moderating influence of fear affect in the above relationship. Here, the efficacy of inhibitory control in subsets of individuals with relatively lower (≤ 51.2 [median]) and higher fear affect (> 51.2) severity varied differently with rsfc between a parcel in right inferior frontal cortex and three other parcels in a) left inferior frontal cortex , b) left lateral temporal cortex, c) right anterior cingulate plus medial prefrontal cortex. While the inhibitory control scaled positively with rsfc in the lower fear affect subset, it showed a converse trend in the higher fear affect subset of individuals, which was consistent across all the pairwise rsfcs. These results elucidate the interindividual differences of functional brain organization of anxious disposition and cognitive control in healthy young adults towards better addressing issues of affect and cognition in this cohort.

Disclosures: S. Kinger: None. **K. Suri:** None. **M. Chakrabarty:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.19/U28

Topic: H.04. Executive Functions

Support: National PKU Alliance Research Grant

Title: Neural basis for emotional control difficulties in individuals with phenylketonuria (PKU)

Authors: M. Z. MARKOLLARI, ***S. CHRIST**;
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Abstract: *Background*: Phenylketonuria (PKU) is a rare inherited disorder associated with a deficiency in phenylalanine hydroxylase, an essential enzyme for the metabolism of phenylalanine (Phe) into tyrosine. As a result, Phe accumulates in the blood and brain. Past research suggests that, even with early and continuous treatment, individuals with PKU experience neurocognitive sequelae including difficulties with cognitive or “cold” inhibitory control. The aim of the present study was to extend this work and examine the neural

underpinnings of affective or “hot” inhibitory control in adults with and without PKU. *Methods*: A sample of 34 adults with PKU (aged 18-36) and a demographically matched comparison group of 32 adults without PKU completed an emotional Stroop task during functional MRI. Each trial presented a picture of a novel face with a happy or fearful affect. The word “happy” or “fear” was superimposed over each stimulus such that the face and word were congruent or incongruent to each other. Participants were to quickly indicate if the facial affect was happy or fearful, ignoring the overlaid words. Following data preprocessing in SPM12, BOLD neural responses were estimated separately for Incongruent (Inc) and Congruent (Con) trials and compared between groups. *Results*: A significant interaction between group and condition was observed for regions in precuneus and ventral anterior cingulate cortex (vACC). In these areas, non-PKU individuals showed inhibition-related deactivation (Inc < Con) while the PKU group showed inhibition-related activation (Inc > Con) [$t(64) > 4.13$, FDR-corrected $p < 0.05$ in both instances]. For other regions in the ventromedial prefrontal cortex (vmPFC) and middle frontal gyrus, the non-PKU group showed deactivation for all trials (Inc + Con) relative to baseline. Yet, the PKU group failed to deactivate these regions to a similar degree [$t(64) > 4.73$, FDR-corrected $p < 0.05$ in both instances]. A significant correlation was also found in the vmPFC between levels of activation and mean Phe [$r = .43$, $p = .014$]. *Conclusions*: PKU individuals showed altered activation patterns in brain areas related to emotional decision making (vACC and vmPFC) as well as autobiographical memory and awareness (precuneus). These regions are also associated with the default mode network (DMN). The DMN is a network of functionally interconnected brain regions thought to play a role in introspection and self-referential activities. This study supports a growing body of research suggesting the DMN may be susceptible to disruption in individuals with PKU, as characterized by failing to effectively disengage these regions during directed cognitive tasks.

Disclosures: M.Z. Markollari: None. **S. Christ:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

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Topic: H.04. Executive Functions

Support: NIH Grant R01DA021421
NIH Grant R01DA058038

Title: Effects of self-reported deficits in executive functioning and length of abstinence on decision-making and delay discounting in heroin and amphetamine users

Authors: E. PSEDERSKA[1], ***J. VASSILEVA**[2];
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Abstract: Background: Substance use disorders significantly impair executive functions (EF) such as decision-making and delay discounting. Some of these functions improve with abstinence. Self-report ratings of daily life deficits in EF (rather than tasks) have higher ecological validity and may better capture symptom severity and impairment. The goal of the current study is to examine how self-reported deficits in EF and length of abstinence affect decision-making and delay discounting in former heroin and amphetamine users.**Method**: We tested 104 participants divided into three groups: 32 abstinent 'pure' heroin users (HU), 41 abstinent 'pure' amphetamine users (AU), and 31 control subjects. The Iowa Gambling Task (IGT) indexed decision-making under ambiguity, the Cambridge Gambling Task (CGT) - decision-making under risk, and the Monetary Choice Questionnaire (MCQ) and the 5-Trial Adjusting Delay Discounting Task (5-Trial Adjusting DDT) measured delay discounting. The Barkley Deficits in Executive Functioning Scale (BDEFS) indexed self-reported deficits in daily life EF. Hierarchical multiple regression analyses evaluated the impact of EF deficits and length of abstinence on decision-making and delay discounting outcomes.**Results**: Control subjects exhibited superior decision-making under ambiguity (IGT) and lower delay aversion and improved risk adjustment (CGT) than both HU and AU ($p < .001$). HU reported significantly more EF deficits than controls ($p = .013$). Deficits in EF predicted steeper delay discounting on the 5-Trial Adjusting DDT among AU ($\beta = .513$, $p = .002$). In contrast, fewer deficits in EF predicted steeper delay discounting on the MCQ among HU ($\beta = -.432$, $p = .013$). Increased length of abstinence was associated with more advantageous decision-making on the IGT but only among AU ($\beta = .469$, $p = .025$).**Conclusions**: Our findings underscore the significant impact of daily life EF on delay discounting, with notable effects among AU. Given the key role of delay discounting as a predictor of treatment retention and relapse vulnerability, these findings suggest that interventions designed to enhance EF could be particularly valuable in developing treatment strategies for amphetamine use disorder. Additionally, our results indicate that prolonged abstinence has a positive effect on decision-making processes related to risk and reward in AU, emphasizing the potential benefits of sustained recovery.

Disclosures: E. Psederska: None. **J. Vassileva:** None.

Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR484.21/U30

Topic: H.08. Learning and Memory

Support: NICHDP50HD105328-01

Title: Understanding behavioral and neural mechanisms of concept learning in autism spectrum disorders

Authors: *Y. CHEN[1], B. HAWKINS[1], A. LOPEZ[2], D. ZEITHAMOVA[3], H. XIE[2], A. VERBALIS[2], L. KENWORTHY[2], C. J. VAIDYA[1];

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Abstract: Autistic children often face challenges in generalizing learned knowledge to novel settings, affecting their learning and adaptive behaviors. This study explores learning mechanisms underlying individual generalization, which is crucial for addressing the real-world adaptive difficulties but has received limited attention. We employed a well-established concept-learning task (Zeithamova et al., 2018) to track individual generalization, which involved out-of-scanner feedback-based training followed by a no-feedback generalization phase coupled with model-based fMRI in 44 teens with Autism (M age: 15.91 ± 1.1, 15 F, Full-IQ: 113 ± 12). Two models of hypothesized learning strategies were fit to individual generalization data: the prototype model, posited to rely on abstract category representations tied to ventral medial prefrontal cortex (vmPFC) and anterior hippocampus; and the exemplar model, posited to rely on representations based on individual category members tied to posterior hippocampus. Categorization accuracy revealed robust learning and generalization, with overall accuracy above chance. Similar to results from healthy adults, we observed a significant linear increase in accuracy across training blocks and a significant typicality gradient during generalization, with most successful generalization to category prototypes and decrease in accuracy as stimuli deviated farther from the prototypes. Model-based analyses revealed that 82% of participants were best fit by the prototype model, suggesting that they successfully extracted the central tendency of each category rather than relying on memorization of individual exemplars. Voxel-wise whole brain search identified regions tracking the prototype regressor in bilateral frontal pole (the medial part of Brodmann areas 9 and 10), right precuneus, right angular gyrus, and bilateral inferior temporal gyrus. No regions tracked exemplar regressors at corrected thresholds and no significant clusters were observed in the hippocampus. These findings highlight the unexpected proficiency of autistic children in concept learning tasks while emphasizing notable differences in associated neural mechanisms. While the majority of autistic teens engaged a prototype-based learning strategy, the prefrontal region we found was anterior and superior to that nominally observed for this type of category learning (vmPFC). Further, hippocampal involvement was not observed for either prototype or exemplar strategies. Further exploration of individual variation in brain activation is needed to fully understand heterogeneity in generalization skills in autistic children.

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Poster

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Topic: H.04. Executive Functions

Support: NIH Grant R15MH126404
Department of Defense W81XWH-19-1-0249

Title: Differential brain activation during a cognitive flexibility task in autistic young adults

Authors: J. DUST[1], H. YOUNESIE[1], M. M. LEE[2], R. TEGIACCHI[1], M. PAKNEJAD[1], ***C. STOODLEY**[3];
[1]American Univ., Washington, DC; [2]Engin., Tufts Univ., Medford, MA; [3]Children's Natl. Med. Ctr., Washington, DC

Abstract: Despite being a core feature of autism, the neural bases of cognitive inflexibility are understudied relative to social behaviors. We have hypothesized that differences in cerebellar structure and function could contribute to less-flexible behaviors in autism (Stoodley & Tsai 2021) and imaging studies show robust cerebellar activation during cognitive flexibility. Here we used functional MRI (fMRI) to evaluate the brain activation patterns during a cognitive flexibility task in young adults with (AG=6, data collection ongoing, 22.0±2.7 yrs, 3 male/3 female) and without (NT=15, 21.8±3.5 yrs, 7 male/8 female) an autism diagnosis. We predicted that the AG would show lower accuracy and reduced cerebellar engagement during the flexibility trials of the Flexible Item Selection Task (FIST; Dajani et al. 2020). The groups were matched on NIH Toolbox Cognition Composite standard scores (NT 107.1±11.7, AG 115.3±5.7), though the NT group scored higher on the Dimensional Card Sort cognitive flexibility subtest (NT 108.0±13.6, AG 92.5±16.0, $p=0.036$). There were no group differences in task performance on either the control or flexibility trials of the FIST. Neuroimaging data were analyzed using a full factorial model in SPM12, including task condition (control, flexibility trials) and group (NT, AG). During control trials, the NT group did not show significantly greater activation than the AG in any regions; the AG showed greater activation than NT in bilateral fusiform, left calcarine, right lingual, and middle occipital gyri ($p<0.005$, $k>25$). During the flexibility trials, the NT>AG comparison revealed significantly greater engagement of a medial cluster in cerebellar lobule IX. Compared with the NT group, the AG showed increased activation in visual areas, left parahippocampal gyrus and hippocampus, bilateral putamen, and the bilateral insula. The medial cerebellar cluster was the only region in the brain showing a significant group x condition interaction. These preliminary analyses reveal different neural underpinnings of cognitive flexibility in autism: the NT group showed greater cerebellar engagement during flexibility trials, while the autistic group relied on hippocampal, basal ganglia, and insula regions to achieve similar task performance. These findings are in line with preclinical and theoretical models proposing that the posterior cerebellar midline is involved in inflexible behaviors in autism.

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Poster

PSTR484: Disorders of Executive Functions and Inhibitory Control

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Topic: H.04. Executive Functions

Support: Brain Institute BaBI Pilot
Brain Institute Transformational Pilot
iTHRIV

Title: Preterm birth disrupts prefrontal function and top-down modulation of visual processing

Authors: *A. RIBIC, E. MCCOY, M. FARIBORZI, J. STINGER, L. DEMIR, O. BUELL; Univ. of Virginia, Charlottesville, VA

Abstract: The process of birth transitions the fetus to extrauterine environment, triggering multiple neurodevelopmental processes that support mature brain function. Advancing this transition through premature birth can disrupt neurodevelopment and result in atypical developmental trajectories. In agreement, over 50% of preterm born infants show cognitive deficits, particularly in the visual processing domain. Previous studies in infants suggest that preterm birth disrupts the function of top-down circuits for visual processing, but it is unknown if this is indeed the case.
To address this, we used preterm born mice to mechanistically define the preterm birth-driven changes in the function of top-down visual processing circuits. Mice born a day early (preterm mice) show normal physical development and intact basic visual function in adulthood. However, preterm mice fail to achieve high levels of performance in a visual discrimination task that is modulated by visual cortex (V1)-projecting anterior cingulate cortex (ACC) neurons. Preterm mice have lower behavioral responses at the onset of training, which transitions into decreased response inhibition at later stages of training. To determine the potential circuit mechanisms of these deficits, we used in vivo electrophysiology and intersectional optogenetics to probe the function of visual and top-down circuits in preterm mice. V1 neurons in naive term and preterm mice are equally selective for task-relevant stimuli. However, this selectivity is maintained in term mice throughout training, but not in preterm mice. Interestingly, V1-projecting ACC neurons develop robust selectivity for task-relevant stimuli during training in term mice, while in preterm mice they show low selectivity for the task-relevant stimuli and disinhibition. In support of reduced inhibition of top-down ACC->V1 circuit, optogenetically identified prefrontal fast-spiking inhibitory interneurons in preterm mice have significantly reduced activity at rest and during task performance. Altogether, our results demonstrate that preterm birth has lasting effects on the function of prefrontal circuits for the modulation of visual processing and highlight their vulnerability to perinatal insults.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.01/U33

Topic: H.07. Long-Term Memory

Support: MRC grant MR/W006804/1

Title: Enhancing memory in humans via MEG-closed-loop Rhythmic Sensory Stimulation (RSS) tuned to the frequency of hippocampal theta oscillations

Authors: *E. MARCANTONI[1], D. WANG[1,2], R. INCE[1], L. T. PARKKONEN[3], S. PALVA[4], S. HANSLMAYR[1];
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Abstract: Hippocampal theta oscillations are considered critical for binding multisensory information into episodic memories. Recent studies suggest that entraining theta oscillations through 4-Hz audio-visual rhythmic sensory stimulation (RSS) can significantly enhance memory performance in humans performing associative memory tasks. This “one-size-fits-all” approach, however, neglects the differences in brain activity among individuals, which could account for the variability in the results. To address this limitation, we developed a new tool designed to estimate the individual hippocampal theta frequency during a memory task and dynamically align the stimulation parameters to it. The key components of the pipeline involve extracting the hippocampal signals during a MEG measurement using an LCMV beamformer. Then, theta activity is separated from the broadband signal applying a Generalized Eigenvalue Decomposition (GED). Finally, the Cyclic Homogeneous Oscillation detection method (CHO) is applied to detect the presence of an oscillation and identify its centre frequency. This frequency is then used to dynamically adjust the flickering frequency of the sensory stimuli during the task. As the first step, we validated the feasibility of the combined use of GED and CHO to reliably estimate the frequency on rodent LFP data, aiming to replicate the well-established correlation between running speed and hippocampal theta frequency. The results indicate that the pipeline was able to replicate previous findings ($R = 0.19$, $p < .001$). After that, the full pipeline, including source reconstruction, has been tested offline on a MEG dataset involving 4-Hz RSS during an associative memory task. Here, our objective was to assess whether the pipeline could accurately identify the entrainment effect induced by the stimulation, with the hypothesis that during RSS the brain should be entrained to the frequency of the external rhythmic force. Our results indicate that hippocampal oscillations during the stimulation were indeed significantly closer to 4-Hz, compared to pre- and post- stimulus time windows (main effect of time $F_{6,120} = 24.99$, $p < .001$, $\eta^2 = 0.315$). Next, we will validate the pipeline in a concurrent MEG-iEEG dataset, to compare the identified frequencies in MEG data with the ground-truth frequency in the hippocampal signal recorded through iEEG, providing deeper information about the accuracy and reliability of our approach. Together, the results suggest that we can reliably extract and detect theta frequency from hippocampal signals in real-time. This tool can be used for closed-loop neurotechnology to interface with brain oscillations.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.02/U34

Topic: H.07. Long-Term Memory

Support: NIH Grant MH120194

Title: Direct electrical stimulation of the human amygdala prioritizes object memory compared to scene memory and differentially engages the anterior vs. posterior hippocampus

Authors: *K. WAHLSTROM[1], J. CAMPBELL[1], M. HOLLEARN[2], M. ADAMEK[3], J. R. SWIFT[4], L. BLANPAIN[5], T. XIE[6], P. BRUNNER[7], S. B. HAMANN[8], A. ARAIN[9], L. N. EISENMAN[10], J. R. MANNS[11], J. T. WILLIE[12], C. S. INMAN[2];
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Abstract: Emotional events are often remembered better than neutral events — a benefit that requires the amygdala. Studies suggest the basolateral amygdala (BLA) in particular, modulates memory-consolidation processes via interactions with downstream brain regions like the hippocampus. Furthermore, direct electrical stimulation of the BLA in humans enhances declarative memory, even for non-emotional events, and this memory enhancement is marked by oscillatory interactions between the BLA and hippocampus. However, the BLA disproportionately projects to the anterior hippocampus compared to the posterior hippocampus, regions that process non-spatial information about objects and spatial information about scenes, respectively. Nevertheless, the premise that the BLA prioritizes some kinds of memories over others has not been directly tested in humans. In the current study we tested whether brief electrical stimulation to the BLA could differentially enhance declarative memory for specific images of objects and scenes. Epilepsy patients undergoing seizure monitoring via intracranial depth electrodes viewed a series of images of neutral objects and scenes, half of which were immediately followed by brief, low-amplitude electrical stimulation of the BLA. Analyses of event-related potentials (ERPs) suggest object and scene images differentially engage the anterior vs. posterior hippocampus. Furthermore, amygdala stimulation elicited no subjective emotional response but enhanced memory for object images but not scene images when patients were given a recognition-memory test the next day. The present study also leveraged direct electrical stimulation of the BLA to interrogate the effective connectivity between the amygdala and hippocampus. Using Single Pulse Evoked Potentials (SPEP) we determined how the

amygdala interacts with the hippocampus to favor memory for objects compared to scenes. Overall, our results suggest that the BLA initiates memory prioritization processes by differentially engaging the anterior vs. posterior hippocampus, providing fundamental insight into how BLA projections to hippocampal regions contribute to the neural dynamics of memory prioritization.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

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Program #/Poster #: PSTR485.03/U35

Topic: H.07. Long-Term Memory

Support: ERC-2018-COG 819814

Title: Hippocampal sensitivity to low-level visual features: human iEEG gamma responses to spatial frequency in the medial temporal lobes

Authors: *A. PERIS-YAGUE[1], M. COSTA[2], G. VAROTTO[2], D. FRANK[2], R. TOLEDANO[3], A. GIL-NAGEL[3], J. SARNTHEIN[4], L. IMBACH[5], D. LEDERGERBER[5], B. A. STRANGE[2]; [1]Univ. Autónoma de Madrid, Madrid, Spain; [2]Univ. Politécnica de Madrid, Madrid, Spain; [3]Hosp. Ruber Internacional, Madrid, Spain; [4]Klinik fur Neurochirurgie, Universitätsspital Zurich, Zurich, Switzerland; [5]Swiss Epilepsy Center, Clin. Lengg, Zurich, Switzerland

Abstract: The hippocampus sits at the top of the visual processing hierarchy and is thought to process cohesive, perceptual information. Thus, it would not be predicted that the hippocampus is sensitive to low-level visual information. In the present study, however, iEEG recordings from 33 medication-resistant epilepsy patients revealed that the hippocampus and adjacent medial temporal lobe structures are sensitive to spatial frequency information. The hippocampus processed different ends of the spatial frequency spectrum in a gradient-like manner along its long axis. Specifically, the anterior hippocampus (n=17) showed a significant gamma response to broadband (BSF) and low-spatial frequency (LSF) face stimuli (54-82hz, 0.33-0.65s; 105-198hz, 0.10-0.26s) whereas the posterior hippocampus (n = 16) showed a gamma response to BSF and high spatial-frequency (HSF) faces (134-170hz, 0.16-0.39s). At earlier stages of the visual processing hierarchy, the perirhinal cortex (n=8) showed a significant gamma response to BSF and HSF stimuli (34-66hz, 0.19-0.45s), consistent with its key role in processing complex perceptual information. The fusiform face area (n=17), a face-sensitive region involved in face identification, elicited an early, significant beta response to BSF and LSF inputs (11-29hz, 0-0.27s) followed by a gamma response to detail-like BSF and HSF (46-138hz, 0.21-0.59s)

information. Our results further presented a significant granger causality effect from the posterior to the anterior hippocampus (n = 7) selective for BSF stimuli (10-26hz, 0.24-0.40s), suggestive of a potential mechanism to reconcile both ends of the spatial frequency spectrum at the hippocampal level. These findings provide direct human electrophysiological evidence that low level visual information is still processed at the apex of the visual processing hierarchy and pinpoint towards a key role of low-frequency oscillations as a potential recompilation mechanism.

Disclosures: A. Peris-Yague: None. **M. Costa:** None. **G. Varotto:** None. **D. Frank:** None. **R. Toledano:** None. **A. Gil-Nagel:** 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 grants from Biocodex, GW Pharma, PTC Therapeutics, UCB Pharma and Zogenix. F. Consulting Fees (e.g., advisory boards); Arvelle/Angelini, Bial, Biocodex, Eisai, Esteve, GW Pharma, Jazz Pharmaceuticals, Pharvaris, PTC Therapeutics, Rapport Therapeutics, Stoke, UCB Pharma, Zogenix and Xenon. **J. Sarnthein:** None. **L. Imbach:** None. **D. Ledergerber:** None. **B.A. Strange:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.04/V1

Topic: H.07. Long-Term Memory

Support: Fixel AI Imaging Genius Grant

Title: Investigating the semantic memory network in drug-resistant epilepsy using stereoelectroencephalography (sEEG)

Authors: *D. JOHNSON[1], A. BABAJANI-FEREMI[2], G. P. KALAMANGALAM[1], A. GUNDUZ[3];
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Abstract: Drug-resistant epilepsy has profound impacts on many cognitive functions. This exploratory study aims to use stereoelectroencephalography (sEEG) to investigate the organization and functionality of semantic memory, the long-term memory for knowledge, in patients with drug-resistant temporal lobe epilepsy (TLE) as the anterior temporal lobes (ATLs) of the brain play a crucial role in this cognitive process. Prior to resection surgery, drug-resistant TLE patients are monitored in an epilepsy monitoring unit (EMU) using invasive sEEG electrodes to precisely locate the brain areas responsible for their seizures. Drug-resistant TLE patients (n=3) were enrolled to participate in a semantic memory task during sEEG monitoring in the EMU. Participants performed a 3-alternative forced-choice (3AFC) semantic judgment task specifically structured to engage the semantic memory network. This task included trials of

synonym judgments to stimulate semantic processing and number judgment trials that served as a contrasting condition. Analysis of the sEEG data facilitated the identification of critical regions of interest (ROIs) involved in semantic memory. We examined local field potentials (LFPs) and the patterns of functional connectivity within these ROIs during task execution. Our findings reveal that the event-related potentials (ERPs) elicited during the synonym judgment trials exhibit distinct characteristics compared to those recorded during the number judgment trials. This study leverages sEEG to provide a detailed view of how epilepsy affects semantic memory, offering crucial insights into the neural basis of cognitive effects of epilepsy. The findings highlight the potential of sEEG as a tool for studying complex cognitive networks in clinical populations and pave the way for future research aimed at mitigating cognitive deficits in epilepsy.

Disclosures: D. Johnson: None. **A. Babajani-Feremi:** None. **G.P. Kalamangalam:** None. **A. Gunduz:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.05/V2

Topic: H.07. Long-Term Memory

Support: R01MH128552

Title: Visual exploration reveals semantic and spatial gradients in the hippocampus

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Abstract: Memories range in precision from highly detailed to vague, but the neural origin of this spectrum is not yet known. Current theories attribute these differences to the anatomical organization of the human hippocampus, with increasing memory resolution in the anterior to posterior direction. However, it remains unclear whether semantic and spatial components of memory share a common anatomical gradient. To address this question, we created a sequence-memory fMRI task that independently manipulates the semantic and spatial attributes of repeating sequences. Behavioral pilot (N = 9) and fMRI participants (N = 14) learned visuospatial sequences of objects and detected mismatching test sequences that differed along spatial and semantic dimensions. Eye-movement tracking was used to differentiate semantic versus spatial memory influences on behavior with high temporal precision. Linear mixed-effects modeling indicates that after learning, participants made predictive eye movements to the next location in the sequence (pilot: $F_{1,8.8} = 8.8$, $p < .001$; fMRI: $F_{1,14.0} = 13.7$, $p < .01$), reflecting spatial memory. Fixation durations increased for unexpected objects but not for objects presented in unexpected locations (pilot: $F_{1,34.6} = 4.8$, $p = .04$; fMRI: $F_{1,12.1} = 105.4$, $p < .001$), reflecting semantic memory. Finally, accuracy on the task varied based on semantic and spatial similarity,

with better detection of mismatching sequences that were either spatially or semantically far from targets (pilot: $F_{1,9.6} = 9.6$, $p = .008$; fMRI: $F_{1,13.8} = 24.7$, $p < .001$). Behavioral findings indicate that the precision of spatial and semantic memory can be differentiated in eye-movement and recognition responses. Additionally, neural pattern similarity decreased along the hippocampal long-axis for both semantic and spatial memory. These findings implicate a common gradient of memory precision in the hippocampus. We will also describe fMRI connectivity analysis results utilizing these behaviors to relate semantic and spatial gradients along the hippocampal long axis to a broader memory precision network.

Disclosures: A.G. Jordan: None. **J.L. Voss:** None. **J.E. Kragel:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Program #/Poster #: PSTR485.06/V3

Topic: H.07. Long-Term Memory

Support: NIH-NINDS R01-NS089729

Title: Hippocampal repulsion as a function of memory similarity and experience

Authors: *D. GRAETZ, W. GUO, S. MIRJALILI, E. WANG, U. MAYR, B. A. KUHL; Dept. of Psychology, Univ. of Oregon, Eugene, OR

Abstract: When experiences are similar (overlapping), this can lead to interference-related forgetting. However, recent research has demonstrated that interference-related forgetting can be minimized via targeted differentiation of activity patterns in the hippocampus (e.g. Hulbert & Norman, 2015; Favila et al., 2016; Wanjia et al., 2021)—a phenomenon we term 'hippocampal repulsion'. Hippocampal repulsion is thought to critically depend on the degree of similarity between overlapping memories (Wammes et al., 2022) and the amount of experience with those memories (Favila et al., 2016), but in ways that are complex and not fully understood (Ritvo et al., 2019). Here, we sought to test for interactions between stimulus similarity and experience in determining hippocampal repulsion. Participants (n = 15) completed an experiment with three phases. During the study phase, participants learned unique associations between images of scenes and objects. Importantly, the scenes were drawn from two categories (beaches and gazebos; 24 scenes per category). For one of the categories (beaches or gazebos, counterbalanced) participants received extensive training on the associations (high experience) whereas for the other category they received more limited training (low experience). Then, during fMRI scanning, participants repeatedly viewed all of the scene images to measure activity patterns in the hippocampus and visual cortical areas. fMRI analyses focused on the hippocampus (separated into CA1 and CA3/dentate gyrus), early visual cortex, and the parahippocampal place area (PPA). For each region, we computed the similarity of fMRI activity patterns for all pairs of scenes, with a coarse division between scenes from the same category

(within-category similarity) vs. scenes from different categories (between-category similarity) and finer-grained distinctions in similarity for scenes within each category. We found that within-category similarity was signficantly lower in CA3/dentate gyrus relative to early visual cortex and PPA. In fact, CA3/dentate gyrus qualitatively inverted the representational structure in visual regions, consistent with prior evidence of hippocampal repulsion. Preliminary analyses indicate that the degree of repulsion in CA3/dentate gyrus depended on stimulus similarity as well as experience, with extensive training accelerating repulsion of similar memories. Planned analyses will relate repulsion effects to memory confusability. Collectively, these findings provide important insight into when and why hippocampal representations become differentiated.

Disclosures: D. Graetz: None. **W. Guo:** None. **S. Mirjalili:** None. **E. Wang:** None. **U. Mayr:** None. **B.A. Kuhl:** None.

Poster

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.07/V4

Topic: H.07. Long-Term Memory

Support: Max Planck Society
The Kristian Gerhard Jebsen Foundation
Liaison Committee between the Central Norway Regional Health Authority and NTNU

Title: Memory deficits in post-COVID condition: relation to structure and function of the medial temporal lobe

Authors: *I. M. KRASOVEC[1,2], T. BONNEVIE[3,4,2], D. REZNIK[5,2], M. BECU[1,2], F. BEYER[6], K. WIRKNER[7], A. VILLRINGER[6], V. WITTE[6], C. F. DOELLER[8,4];
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Abstract: Post-COVID condition (PCC; “Long Covid”) is a multi-systemic condition with diverse clinical presentations. A subset of PCC patients report neurocognitive symptoms, including subjective memory deficit and anosmia, the loss of the sense of smell. These specific deficits may be related to a COVID-related vulnerability of the medial temporal lobe (MTL), a

brain region associated with both memory and olfactory function. It is of clinical relevance to contextualize subjective memory deficit in PCC using established measures of objective memory performance, as well as to advance the understanding of the underlying neural mechanisms and neuropathology. Here, we address, in PCC cases relative to controls, the relationship between anosmia, memory symptoms, and objective memory performance. Next, we assess grey matter (GM) volumes and functional activity of the MTL in relation to subjective and objective memory deficit. Study participants were enrolled in a cohort study and characterized in terms of COVID disease presentation, symptom burden and memory performance. Participants underwent structural and functional 3T MRI and performed an in-scanner memory paradigm. The PCC group (n=68) underperformed relative to the control group (n=26) in spatial memory, as assessed by the well-established Four Mountains task. In cases, increased subjective memory deficit was related to subjective anosmia, but not to spatial memory performance. Cases and controls did not differ in MTL grey matter volume when correcting for age, sex, and intracranial volume. We found no relationships between GM volume in the MTL and objective memory deficit, subjective memory deficit, or anosmia in cases. Our next step will be to assess whether memory-related functional activity in the MTL is altered by COVID status, and how it relates to memory deficits and anosmia. COVID-related changes in functional activity of the MTL, even in absence of GM volume changes, could possibly reflect neuropathology underpinning clinically observed complaints associated to PCC.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

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Program #/Poster #: PSTR485.08/V5

Topic: H.07. Long-Term Memory

Title: A surface-based probabilistic atlas of the anterior medial temporal lobes: temporopolar, entorhinal, perirhinal, and parahippocampal cortices

Authors: I. FAUL, E. AYMOND, Z. CONNER-BENNETT, S. GRAZIOSE, R. KOLLURU, A. NWACHA, J. PARK, A. SAHIBUL, *B. DEEN;
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Abstract: The anterior medial temporal lobes (aMTL) contain a set of cortical areas providing an interface between association cortex and the hippocampal formation, thought to be critical for long-term memory. These include entorhinal cortex (ER), with direct connections to the hippocampus, as well as perirhinal (PR) and parahippocampal cortex (PH), with connections to ER. A less well-characterized component of this system is temporopolar cortex (TP), a primate-specific brain area situated just anterior to PR, with a similar pattern of inputs to ER. Identifying the anatomical locations of these areas in individual human brains is a critical precursor to

studying their function. However, existing atlases of aMTL areas have several limitations: 1) they are derived from relatively small sample sizes; 2) they typically do not include TP; and 3) they are volume-based, and subject to potential inaccuracies of volumetric normalization methods. Here, we develop a surface-based probabilistic atlas of aMTL regions TP, PR, ER, and PH derived from hand drawings of gross anatomical boundaries in N = 100 young adult participants. Data were .7mm-resolution T1-weighted anatomical MR images from the Human Connectome Project (HCP) dataset. Regions were hand-drawn bilaterally on volumetric images using a protocol based on previously described sulcal and gyral landmarks corresponding to cytoarchitectonic boundaries between areas. Regions were then converted to standardized cortical surface coordinates (fsLR space) using the HCP normalization approach: cortical surface reconstructions for individual participants were generated using Freesurfer; regions were resampled to individual surfaces using ribbon-constrained mapping; and individual surfaces were normalized to fsLR space using multimodal surface matching. Lastly, data were combined across participants to produce a probabilistic atlas specifying the likelihood of each area existing at a given surface coordinate. This work provides a useful tool for researchers studying the anatomy and function of aMTL areas, and especially the poorly understood area TP, using surface-based analysis.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Topic: H.07. Long-Term Memory

Support: Wellcome Principal Research Fellowship (222457/Z/21/Z) “Neural mechanisms of memory & prediction, finding structure in experience”
Sainsbury Wellcome Centre PhD Stipend

Title: Medial temporal high frequency gamma power distinguishes between active rehearsal and wakeful rest in a narrative episodic memory task

Authors: *N. MAUG[1], Y. HE[1], D. BUSH[2], N. BURGESS[1];
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Abstract: Active rehearsal refers to the cognitive process of consciously repeating task-relevant information to maintain it active in working memory. When implemented with the aim of committing sequential and relational information to long-term memory, this strategy is associated with sustained entorhinal and hippocampal activity (Schon et al. 2004) and hippocampal gamma amplitude coupling to frontal theta phase (Daume et al. 2024). Likewise, wakeful rest after memory encoding is known to benefit episodic memory (Dewar et al. 2012)

and to be associated with increased post-stimulus hippocampal activity (Ben-Yakov and Dudai, 2011). This raises the question of whether the neural dynamics associated with conscious working memory processes and offline consolidation processes, such as sharp-wave ripple associated replay, in medial temporal lobe networks overlap or whether they are discernible. We analysed the neural dynamics of participants (n=23) after viewing short narratives in an MEG scanner. The semi-naturalistic narrative task consisted of image sequences accompanied by short texts, each followed by a 5-second uninstructed rest period. Participants self-reported the extent to which they engaged in active rehearsal during the rest period at the end of the task. Participants that did not report actively rehearsing in any rest periods had greater power in the 70-140 Hz high gamma band localised to the right anterior medial temporal cortex. Neither episodic memory performance nor working memory capacity differed significantly by self-reported active rehearsal extent (n=15 rehearsal on some/all trials, n=8 none), suggesting that active rehearsal was not a compensatory strategy for reduced working memory capacity. In summary, we show that wakeful rest and active rehearsal dynamics are discernible using MEG, with greater high gamma during wakeful rest. Future analyses will investigate whether more nuanced phase-amplitude relationships are indicative of active rehearsal. These findings highlight the importance of self-reported cognitive strategies for understanding memory function in more ecologically valid contexts, and the importance of considering interactions between working and episodic memory processes in the medial temporal lobe in episodic memory tasks.

Disclosures: N. Maug: None. **Y. He:** None. **D. Bush:** None. **N. Burgess:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

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Program #/Poster #: PSTR485.10/V7

Topic: H.07. Long-Term Memory

Title: Optimizing a within-trial episodic memory paradigm for hippocampal network-targeted non-invasive stimulation

Authors: *P. F. AGRES, A. G. JORDAN, R. B. BAUDO, J. L. VOSS;
Neurol., Univ. of Chicago, Chicago, IL

Abstract: Hippocampal indirectly targeted stimulation (HITS) is a method for modifying hippocampal function by applying transcranial magnetic stimulation (TMS) to superficial cortical regions within the hippocampal network. HITS has been demonstrated to increase functional connectivity within the hippocampal network and improve behavioral performance on hippocampal-dependent memory tasks. However, individual differences in hippocampal network connectivity and memory performance have been observed following HITS. One approach to address this heterogeneity is to identify HITS parameters that drive hippocampal function in each individual via optimization. Different HITS stimulation rhythms (e.g., theta burst), intensities, or target locations may be evaluated across trials in individuals. To accomplish this, it would be

beneficial to measure the effects of HITS on hippocampal network function on individual, brief, self-contained memory trials. In contrast, typical memory tests involve lists of memoranda tested in aggregate. To develop a within-trial episodic memory test suitable for HITS optimization, we adapted a novel version of a spatial reconstruction task that has been shown to depend on the hippocampus. On each trial in this task, subjects learn the spatial arrangement of a set of objects and then attempt to identify a subset of objects with swapped positions after a brief delay. The entire study, delay, and test phase for each trial lasts < 30 seconds. In a group of N=6 healthy control subjects (ages 22-36), we found that, following a brief accommodation period, accuracy was stable for each individual subject over the course of ~100 trials. We varied task difficulty by increasing the number of swapped objects and found that accuracy varied with difficulty, as expected (number of item swaps; all p's < .01). To avoid ceiling and floor effects, we developed and tested two versions of the task (N=6 and N=3 per group) that varied the overall number of objects used for the memory set in each trial (set size) and found that, as expected, accuracy varied with set size (t = 2.33, p < .05). For most subjects, a larger set size was necessary to avoid the potential for ceiling effects. Our results indicate that the brevity of the task, stability of performance across trials, and modulation of subject performance with task difficulty make this novel paradigm suitable for experiments that optimize HITS to impact within-trial memory performance. We will discuss the effects of HITS using standard parameters on task performance in an independent group (N=8), and the relevance of these effects for future studies to optimize HITS for each individual using this task.

Disclosures: P.F. Agres: None. **A.G. Jordan:** None. **R.B. Baudo:** None. **J.L. Voss:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Topic: H.07. Long-Term Memory

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Simons Foundation Collaboration on the Global Brain (542941)
Caltech NIMH Conte Center P50MH094258)
Josephine De Karman Foundation Fellowship

Title: The geometry of task representations in human frontal cortical neurons is predictive of instructed task switching costs.

Authors: *H. COURELLIS[1], D. DENG[2], I. SKELIN[3], T. A. VALIANTE[3], A. N. MAMELAK[4], U. RUTISHAUSER[5];
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Abstract: The process of switching between tasks occurs countless times throughout the day for an individual. Every instance of switching is accompanied by a cost, a decrease in task accuracy and/or speed immediately after switching that rapidly fades away. Though this switch cost is reducible when preparatory time is given after instructions, an irreducible switch cost is always present the first time one engages in a task when switching from a different task. The presence of switch costs in animals is debated, but is a prominent aspect of human cognition. The neural mechanisms that generate switch costs remains unknow and are hotly debated. Theories center around two possible causes: reconfiguration and lingering activity (inertia) related to the prior task. Some evidence from intracranial recordings exists supporting these proposed explanations, which indicate a key role of the medial frontal cortex (MFC). However, the neurophysiological basis of switch costs remains elusive. To study the dynamics exhibited by neurons following instructed task switching and to arbitrate between different theories of switch costs, we recorded the activity of large populations of single neurons in the MFC of neurosurgical patients performing a task with frequent instructed switching between a categorization (cat) task, and a memory (mem) task. Task instructions were given once at the start of each block, and needed to be remembered for the ensuing 8 trials where patients were presented with a visual stimulus and provided a binary response (either yes or no) in accordance with the current rule. Patients (36 total) completed 58 sessions of this task, performed accurately (93.7% cat, 85.6% mem), and exhibited profound switching costs in their reaction time on switch trials (40.5% cat, 33.0% mem). Responses of single neurons were recorded using hybrid clinical-research during these sessions, yielding 841 well isolated neurons from the dorsal Anterior Cingulate Cortex (dACC, 415 neurons) and pre-Supplementary Motor Area (preSMA, 426 neurons). We find that neurons in both regions encode the current task context during pre-stimulus baseline periods. However, in dACC immediately following a task switch, context-coding neurons persistently representing the previous task context were predictive of higher switching costs on the upcoming trial. Stimulus-related variables were also less decodable from dACC neurons during stimulus presentation on switch trials and in a performance-dependent manner. Thus, both the task-set inertia and reconfiguration theories are consistent with aspects of our data, particularly when considering the task representation in the dACC.

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Poster

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Program #/Poster #: PSTR485.12/V9

Topic: H.07. Long-Term Memory

Support: NIH Grant U01NS117839

Title: Representation of decision criterion in human single neurons during recognition memory

Authors: *E. LAYHER[1,2], M. B. MILLER[3], A. N. MAMELAK[1], I. SKELIN[4,5], T. A. VALIANTE[4,5,6], U. RUTISHAUSER[1];
[1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]University of California, Santa Barbara, CA; [3]Univ. of California, Santa Barbara, CA; [4]Krembil Brain Inst., Toronto Western Hosp., Toronto, ON, Canada; [5]Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, ON, Canada; [6]Division of Neurosurgery, University of Toronto, Toronto, ON, Canada

Abstract: The goal of this study is to differentiate neural mechanisms associated with memory versus decisional processes during recognition memory at the single-unit level. We created a recognition memory paradigm with manipulations of familiarity strength and decision criteria in a fully crossed 2x2 design. Familiarity strength was manipulated by presenting images either once (hard difficulty condition) or twice (easy difficulty condition) during the study phase. To alter decision criteria, participants earned points for correct responses, but lost points for critical errors, which alternated between false alarms (conservative criterion condition) and misses (liberal criterion condition). Neural activity associated with memory processes should only be affected by difficulty manipulations, whereas criterion manipulations should reveal neural activity associated with decisional processes. We administered the task to 9 epilepsy patients with depth electrode implants, which allowed for single-unit recordings across regions in the medial temporal lobe and medial frontal cortex. Patients performed better in the easy (d_a = 1.38) versus hard (d_a = 0.96) difficulty condition and shifted criteria on average between criterion conditions (Δc_a = 0.83). Our analyses focus on "memory-selective" (MS) neurons, which show firing rate differences between hit and correct rejection trials during the test stimulus presentation period in at least one test condition ($p < .025$). MS neurons are classified as "familiarity-selective" (FS) when the firing rate is greater for hits and "novelty-selective" (NS) when correct rejections show greater firing rates. Of the 937 isolated units, 118 were MS (60 FS, 58 NS). For each MS neuron, we conducted single-unit ROC analyses between hit and correct rejection trials per test condition. When patients shifted their criteria, FS neurons showed greater area under the curve (AUC) differences for the easy versus hard difficulty condition (ΔAUC = .039, $p < .05$) and for the conservative versus liberal criterion condition (ΔAUC = 0.11, $p <$ .001). Some FS neurons only exhibited significant changes in AUC when task difficulty changed, suggesting an association with memory processes. Other FS neurons only exhibited AUC changes between criterion manipulations, indicating that these neurons are response bias-selective. NS neurons did not show mean AUC differences between task difficulty or criterion manipulations, though many units appeared affected by only one manipulation type. These preliminary results reveal that this paradigm can distinguish between neurons involved in memory versus decisional processes of recognition memory.

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Poster

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Topic: H.07. Long-Term Memory

Support: NIH Grant U01NS117839
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Title: Persistent neural activity during working memory maintenance predicts long-term memory formation in the human hippocampus

Authors: *J. DAUME[1], J. KAMINSKI[2], Y. SALIMPOUR[3], A. GÓMEZ PALACIO SCHJETNAN[4], W. S. ANDERSON[3], T. A. VALIANTE[4], A. N. MAMELAK[1], U. RUTISHAUSER[1,5];
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Abstract: Working Memory (WM) and Long-Term Memory (LTM) are often viewed as separate cognitive systems that interact when encoding new memories. However, the neuronal mechanisms of these interactions remain poorly understood. We recorded single neurons in the human medial temporal lobe (936 neurons across 47 sessions) while patients undergoing surgery for pharmacoresistant epilepsy treatment held novel items in WM. The WM task was followed by a subsequent LTM recognition test. We identified category-selective cells in hippocampus and amygdala which remained persistently active during the delay period of the WM task and whose activity was indicative of WM content, load, and quality. These cells have been shown to be involved in the WM storage of newly encoded information (Daume et al, Nature, 2024). In the hippocampus, but not the amygdala, the strength of category-selective cells during the maintenance period predicted the success of episodic memory formation. Hippocampal category cells fired more strongly during the WM delay period for later remembered than forgotten images when the neurons' preferred category was maintained in WM and the patients' reported confidence was high. No effects were found for visually evoked activity during encoding, unpreferred categories, or when the reported confidence was low. Category neurons were further independent of memory-selective neurons whose activity were indicative image familiarity during the LTM retrieval phase. These memory-selective neurons were more strongly activated when persistent activity of simultaneously recorded category neurons happened to be high in the previously performed WM task. Together, these results show a direct link between the activity of neurons during WM and subsequent declarative memory strength in the hippocampus, revealing the single-neuron mechanisms involved in interactions between WM maintenance and LTM formation.

Disclosures: J. Daume: None. **J. Kaminski:** None. **Y. Salimpour:** None. **A. Gómez Palacio Schjetnan:** None. **W.S. Anderson:** None. **T.A. Valiante:** None. **A.N. Mamelak:** None. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.14/V11

Topic: H.07. Long-Term Memory

Support: U01NS103792
U01NS117839
BCS-2219800

Title: Elucidating the role of sensory cortical areas in short-term memory

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Abstract: Background
Working memory, characterized by the ability to maintain information for a brief period, is a hallmark function of higher cortical areas, such as the prefrontal cortex. Traditionally, sensory cortical areas, like the inferior temporal (IT) cortex known for visual processing, have been considered to primarily encode and transmit sensory information without significantly contributing to higher cognitive functions. In this study, we propose that sensory regions can participate in higher cognitive functions through feedback connections from higher-level cortical areas.
Methods
Single-neuron activity data recorded from ten epilepsy patients (70% female, mean age +/- stdev; 40.0 +/- 11.7 years old) were included in the current study. Informed consent was obtained from the participants, and all the protocols were approved by the Institutional Review Boards of Cedars-Sinai. The participants engaged in the Sternberg task, a well-known cognitive task that requires working memory. In each trial, participants were instructed to memorize a single picture presented for one second (encoding period), followed by a delay period of at least 2.5 seconds, after which they determined whether a probe picture matched the previously shown image. Across all participants, we isolated 143 putative single neurons from the IT. Of these, 33 IT neurons were selective to the visual stimuli and included in the analysis. To mirror the experimental data, we constructed an artificial spiking recurrent neural network (RNN) model and trained it to perform a simplified version of the Sternberg task. The model contained spiking model neurons recurrently connected to one another to mimic the structure of the cortex. Five RNNs were trained, each containing 400 model neurons, and we identified units exhibiting firing patterns closely resembling those observed in IT cells.
Results and Conclusion
Both human participants and artificial network models demonstrated high task accuracy, with humans achieving 98.3% +/- 1.50% and networks 90.0% +/- 6.44%. Both IT neurons and IT-like model neurons exhibited stimulus selectivity during encoding, followed by a return to baseline levels during the delay period. During the probe period, IT neuron firing rates significantly rose when the probe image differed from the encoding image, similar to IT-like model neurons,

indicating potential engagement in working memory tasks. These findings challenge the traditional view of IT neurons as solely sensory encoders, highlighting the dynamic nature of neural processing in sensory regions.

Disclosures: R. Kim: None. **N. Rungratsameetaweemana:** None. **J. Daume:** None. **C. Reed:** None. **A.N. Mamelak:** None. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

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Program #/Poster #: PSTR485.15/V12

Topic: H.07. Long-Term Memory

Support: BRAIN Initiative U01NS117839

Title: Neural dynamics underlying memory formation of narrative stories

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Abstract: The human medial temporal lobe (MTL) plays a critical role in converting continuous sensory experience into discrete and memorable events, which is essential for episodic memory formation. Cognitive boundaries are key transitions in context that help organize continuous experience into discrete mnemonic episodes. While the role of the MTL neurons in cognitive boundary detection and subsequent memory formation in the visual domain has been established (Zheng et al, 2022), whether MTL neurons play a similar role in the auditory domain remains unclear. This study investigates the neural dynamics involved in recognizing boundaries and familiarity cues during auditory narrative processing, offering insights into auditory memory formation. Participants are individuals with drug-resistant epilepsy (n = 6, in total 8 recording sessions), who are implanted with depth electrodes for seizure monitoring. We record both single unit activity and local field potential signals as participants engage in a structured auditory memory task, listening to seven short stories repeated six times and freely recalling the content of the stories. We found that about 10% of neurons, termed "word-selective cells", increase their firing rates in response to specific words, that encapsulate key points and serve as markers of cognitive boundaries in the story. Besides, we observe that 19% of neurons (“type I familiarity cells”) either increase or decrease their firing rates when participants repeatedly listen to the same story with their baseline firing rates remaining constant across repetition. We also observe that 25% of neurons (“type II familiarity cells”) show an increase in the predictability of neuronal spiking as a function of story repetition, quantified as increases in the mutual information between the firing rates and their subsequent rates 250 milliseconds later. These two groups of neurons, with firing rates modulated across repetitions of story listening are likely

crucial for recognition of familiar stimuli. In sum, our study provides single neuron evidence for cognitive boundaries and familiarity signals during story listening in the human brain and strengthens our understanding of neural mechanisms underlying the formation of auditory narrative memory.

Disclosures: A. Flores: None. **V. Wadia:** None. **A. Mamelak:** None. **J. Zheng:** None. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.16/V13

Topic: H.07. Long-Term Memory

Support: BRAIN initiative U01NS117839

Title: Towards a single-neuron substrate of pattern separation in the human hippocampus

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Abstract: Humans can form distinct new memories despite having many very similar memories already encoded. The hippocampus may achieve this via pattern separation, yet its applicability and neuronal correlates in humans remain debated. Here we recorded the single-neuron activity in intractable epilepsy patients during a recognition memory task. Newly discovered "memory selective" (MS) cells in the hippocampus respond differently to familiar and novel stimuli. We hypothesized that MS cells exhibit pattern separation signatures, e.g., decorrelated responses to similar stimuli. First, we aimed to establish reliable similarity metrics for visual stimuli used in the task. For this, we compared cosine similarity between several deep neural network (DNN) feature vectors for a pair of images with human similarity ratings from online participants who performed multi-arrangement tasks. We found that deep features of the ViT-based model DINOv2 outperform all other models in predicting human perceptual similarity. Then, we explored if the derived similarity metric could explain the memory behavior of epilepsy patients. We hypothesized that the probability of incorrectly recognizing new images as “old” (“false alarms”) is at least partially a function of the new images being similar to previously studied images. To test this, for each new image we correlated the false alarm rate against the minimum cosine similarity between DNN feature vectors for this image and all images presented during learning. We found that DINOv2 cosine similarity significantly correlates with the false alarm rate (Spearman rho: 0.38, $p<0.001$) suggesting that new images that are more similar to those previously studied are more likely to be mistakenly recognized as “seen before”. Next, we

selected hippocampal MS neurons and assessed their activity during false alarm trials. Single-neuron ROC analysis showed that MS neurons could discriminate between “true” and “false” old stimuli (ROC AUC values significantly higher than 0.5, $p<0.001$, one-side t test). This supports our hypothesis that MS neurons can discriminate between highly similar visual stimuli, i.e., are capable of performing pattern separation. On a population level, we observed a strong negative correlation between MS cells response magnitude and stimulus false alarm rate (Spearman rho=0.23, p=0.0039), suggesting that population vector magnitude might be a coding mechanism for distinguishing between true memories and similar “lures”. Future work is required to validate if these mechanisms can support neuronal pattern separation, but this study marks pivotal first steps toward identifying single-neuron correlates of this process.

Disclosures: N. Kurilenko: None. **C. Reed:** None. **W.S. Anderson:** None. **T.A. Valiante:** None. **A.N. Mamelak:** None. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Topic: H.07. Long-Term Memory

Support: NIH Grant U01NS117839
Simons Collaboration on the Global Brain
NIH Grant T32 NS105595-01A1

Title: Disentangling visual and semantic information in human medial temporal lobe neurons during episodic memory

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Abstract: The human medial temporal lobe (MTL) sits at the apex and confluence of multimodal information streams, including semantic information from the anterior temporal lobe and visual information from the ventral visual stream. The MTL binds disparate features from these information streams together into a coherent episodic memory. Previous studies have shown differential contributions of visual and semantic information to human similarity judgments during perception and memory, but the neural correlates of these differential contributions have not been examined. Here, we use a dataset of single-unit recordings from human MTL (1701 neurons across 59 patients and 87 sessions) during a recognition memory task for images to examine how the representation of information in the MTL changes during learning and recognition memory. To distinguish visual and semantic representations, we use representational similarity analysis to compare neural representations and visual (DINO, VGG),

semantic (SGPT), or visuo-semantic (CLIP) representations derived from deep neural networks. We find that during learning, the neural representation is better explained by visual models and during recognition memory, the neural representation is better explained by semantic models. Examining the time course of these contributions relative to stimulus onset shows that semantic information is represented later than visual information. We then investigated at the single-neuron level which neurons contribute this late semantic information. Our results reveal that visual and semantic information can be disentangled at the neural level during processing of images for learning and recognition memory.

Disclosures: K.J.M. Le: None. **J. Minxha:** None. **A.N. Mamelak:** None. **P. Perona:** A. Employment/Salary (full or part-time):; Amazon Web Services. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Program #/Poster #: PSTR485.18/V15

Topic: H.07. Long-Term Memory

Support: W911NF-23-2-0067
W911NF-22-2-0148

Title: Complex top-down signaling dynamically shapes information processing in human single neurons

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Abstract: One of the hallmarks of human decision making is the ability to rapidly switch between different goals and flexibly adapt to new task demands as they are presented. One open question is how top-down information, such as task instructions, influences sensorimotor integration across higher-level and lower-level brain areas, which could rely on a feedback mechanism. To investigate this, we asked intracranially implanted human epilepsy patients to perform a flexible decision making task (192 trials) in which they had to view a sequence of two stimuli of the same category (faces, cars, fruit, animals) and compare them along a target axis (color, age, numeracy, identity). A key design feature was that trial instructions were either presented early, before stimuli, or late, after the first stimulus. This manipulation orthogonalized encoding of bottom-up stimulus features from flexible top-down encoding during the presentation of the first stimulus while keeping the second stimulus as a control. We obtained 435 neurons across ventromedial prefrontal cortex, amygdala, pre-supplementary motor area (preSMA), dorsal anterior cingulate cortex (dACC), hippocampus, and inferotemporal cortex

(IT). We observed a significant number of neurons in hippocampus and IT which encoded stimulus categories both while viewing stimuli as well as when reading trial instructions, which was also reflected in successful decoding of stimulus category in these regions. However, a cross-condition generalization analysis revealed that the populational code for stimulus category was more preserved in IT than in hippocampus when comparing the late versus early instruction conditions, suggesting a role for top-down instructions in reshaping bottom-up coding in hippocampus. Importantly, we found that preSMA neurons encoded task demands expressed in instructions both at the time of decisions but also earlier at the time of reading task instructions, suggesting a role for preSMA in the early encoding of high-level task demands, beyond motor preparation alone. Overall, these results provide a novel account for how task instructions reshape the activity of neural populations in the human brain, and how top-down and bottom-up encoding are flexibly integrated during decision-making.

Disclosures: N. Rungratsameetaweemana: None. **T. Aquino:** None. **R. Kim:** None. **C. Reed:** None. **A.N. Mamelak:** None. **U. Rutishauser:** None.

Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Program #/Poster #: PSTR485.19/V16

Topic: H.07. Long-Term Memory

Support: NIH U01NS117839
HHMI
SCGB

Title: A shared code for perceiving and imagining objects in the human brain

Authors: *V. S. WADIA[1], A. BROTMAN[2], C. REED[1], J. CHUNG[1], L. M. BATEMAN[1], D. Y. TSAO[3,4], U. RUTISHAUSER[1,5];
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Abstract: Mental imagery is a remarkable phenomenon that allows us to remember previous experiences and imagine new ones. Animal studies have yielded rich insight into mechanisms for visual perception, but the neural mechanisms for visual imagery remain poorly understood. Here, we first determined that 80% of visually-responsive single neurons in human ventral temporal cortex (VTC) used a distributed axis code to represent objects, using that code to reconstruct objects and generate maximally effective synthetic stimuli. We then recorded responses from the same neural population while subjects imagined specific objects and found that a substantial fraction of axis-tuned VTC neurons recapitulated the visual code. In addition, we explored the dynamics of this code i.e., how this code changes during the encoding of specific familiar

identities and how brain-wide recall events are coordinated at single neuron resolution. Our findings reveal that visual imagery is supported by reactivation of the same neurons involved in perception providing single neuron evidence for the implementation of a generative model in the human brain, and that the integration of mnemonic information about a specific object changes its representation within the same neurons.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

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Program #/Poster #: PSTR485.20/V17

Topic: H.07. Long-Term Memory

Support: NIA R56AG068149
NIA RF1AG039103

Title: Pupil size increases reflect greater hippocampal activity and better memory accuracy in young and older adults

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Abstract: Task-related pupil dilation has been linked to numerous cognitive processes such arousal, attention, and cognitive demands. However, less is known about pupillary responses in relation to memory processes, especially in the context of source memory paradigms. Neuroimaging studies examining neural correlates of pupil dilation have focused almost exclusively on the locus coeruleus (LC), a small nucleus in the brainstem which mediates a general arousal response. Considering that the hippocampus receives robust and direct noradrenergic projections from the LC, it is reasonable to suspect that pupil dilation also covaries with hippocampal activity during memory retrieval. Surprisingly, this hypothesis remains largely unexplored. In the present study, young and older adults underwent fMRI with simultaneous eye-tracking as they completed a source memory task. During encoding, participants viewed words paired with images of objects or scenes. At retrieval, participants viewed studied and unstudied words and made judgments about the associated image categories. Pupillometry data demonstrated that correct source memory judgments were linked to larger pupil size than previously studied items that received an incorrect judgment. In turn, incorrectly judged studied items were associated with greater pupil size than correctly rejected novel items. Given these findings, we performed three sets of linear mixed effects (LME) analyses. First, binomial generalized LME was employed to examine the relationship between pupil size and memory accuracy for previously studied items (correct vs. incorrect judgments), confirming that correct

memory judgments were associated with greater pupil size. Second, three generalized LMEs (separate LMEs for hippocampal head, body, and tail) examined whether hippocampal fMRI BOLD responses were related to memory accuracy. The analyses identified greater activity in hippocampal body and tail during correct compared with incorrect judgments. The last set of LME models assessed whether hippocampal BOLD activity (for correct trials only) covaried with pupil size. The analyses revealed robust positive relationships between BOLD activity and pupil size in all hippocampal regions and in both age groups. These results provide novel evidence that pupil dilation correlates with recollection-related hippocampal neural activity in both young and older adults.

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Poster

PSTR485: Human LTM: Medial Temporal Lobe

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR485.21/V18

Topic: H.07. Long-Term Memory

Title: Joint feature representation in visual cortex and its relationship to medial temporal lobe in scene memory

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Abstract: Our memory for scenes draws on our perceptual and memory systems. Memory processes can be probed by examining the synchrony of information within activity patterns of visual regions and the hippocampus. Here we derive the degree of joint visual feature representation by measuring how the visual cortex represents different aspects of a scene on a trial-by-trial basis and examine its relationship with Medial Temporal Lobe (MTL) activation. We analyzed fMRI responses collected as eight subjects participated in a continuous scene recognition task over 30-40 scan sessions from the Natural Scene Dataset. For visual regions processing places, faces and bodies, we quantified the ability to decode place, face and body aspects of a scene, and generated an overall metric of joint feature representation. We found that greater joint feature representation is associated with increased activation in widespread regions of perirhinal cortices. For previously unseen (i.e., new) trials, the hippocampus shows greater activation for greater joint feature representation among visual regions, while no such relationship was found for old trials. Our results show that joint feature representation across the visual system interacts with hippocampal activity based on a scene's memory history.

Disclosures: Y. Bai: None. **M.N. Coutanche:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.01/V19

Topic: H.08. Learning and Memory

Title: Exploring the Impact of Drug-Associated Memories in the Dentate Gyrus on Drug-Seeking Behavior

Authors: *W. F. WADE[1,2], L. H. EDWARDS[2], M. R. WILSON[2], S. A. ARORA[2], L. PAPANIKOLAOU[2], H. K. ASGARALI[2], P. CHATTERJEE[2], S. CAÑUELAS DEL VALLE[2], A. STRATMANN[2], M. M. MCANESPIE[2], S. L. GRELLA[2];
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Abstract: Addiction is characterized by a continual propensity to relapse. Relapse-prevention strategies aimed at reducing the likelihood and severity of relapse following abstinence, focus on reducing cravings that lead to drug-seeking. Factors precipitating drug-seeking include exposure to drug-related cues, to the drug itself, and to stress. We are interested in the contribution of drug-related memories in drug-seeking behaviors. Memories are thought to be stored as representations (engrams) in the hippocampus. Recent technological advances have given us the ability to genetically tag and manipulate memories in mice, such that we can reactivate them with light post-encoding. To investigate the role of these memories in promoting or protecting against relapse, we tagged dorsal dentate gyrus (dDG) cells involved in encoding a cocaine-related memory using a Tet-tag system to express ChR2 driven by the c-Fos promoter, in male and female c57BL/6 mice. Conditioned place preference (CPP) has been used to study the rewarding aspect of drugs and the reinstatement model has been specifically used to study relapse. We carried out multiple CPP experiments to assess whether a cocaine-tagged memory could be used in place of cocaine during conditioning and during reinstatement thus exploring whether conditioning or reinstatement could be primed via the memory of the drug in comparison to the drug itself. We also assessed whether these effects were additive.

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Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.02/V20

Topic: H.08. Learning and Memory

Title: Fear Engrams in the Dorsal Dentate Gyrus During Fear Learning and Fear Generalization: Implications for Post-Traumatic Stress Disorder

Authors: *A. TULLURI, L. PAPANIKOLAOU, M. MCANESPIE, H. ASGARALI, L. H. EDWARDS, A. STRATMANN, A. DAKI, Z. AHMAD, M. A. MACKEY, S. L. GRELLA; Loyola Univ. Chicago, Chicago, IL

Abstract: A hallmark symptom of PTSD is fear generalization, where acquired fear responses to a particular stimulus or context are transferred to other stimuli and contexts. This may stem from memory-updating impairments involving a failure to remap trauma-related memory traces in the presence of novel information (e.g., safety signals), and the persistent recall of these traces in the presence of non-trauma-related contexts / stimuli. Here, we assessed these potential remapping deficits at the engram level in wildtype male and female c57BL/6 mice. The stability and flexibility of fear-related memory traces in the hippocampus were examined using a viral-based neuronal tagging strategy (Tet Tag system) combined with immunohistochemistry and fluorescent confocal microscopy. We also examined whether fear generalization or remapping deficits could be predicted using a behavioral pre-screening method associated with the acoustic startle reflex where mice were parsed into susceptible and resilient populations based on their response to a startle stimulus delivered acoustically.

Disclosures: A. Tulluri: None. **L. Papanikolaou:** None. **M. McAnespie:** None. **H. Asgarali:** None. **L.H. Edwards:** None. **A. Stratmann:** None. **A. Daki:** None. **Z. Ahmad:** None. **M.A. Mackey:** None. **S.L. Grella:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

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Program #/Poster #: PSTR486.03/V21

Topic: H.08. Learning and Memory

Support: NIH Grant ZIAMH002784

Title: Cardiovascular reactivity as a measure of emotional arousal following ablation of adult-born hippocampal neurons

Authors: *A. SWIERCZ[1], H. A. CAMERON[2];
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Abstract: Optimal performance in difficult discrimination tasks requires intermediate levels of emotional arousal. Interestingly, performance in difficult discrimination tasks is impaired following elimination of adult-born neurons in the dentate gyrus, suggesting a potential link between hippocampal neurogenesis and emotional arousal. This possibility is consistent with findings that emotional arousal decreases the range of cue utilization, and that neurogenesis seems to direct attention toward multiple stimuli. Sharp-wave activity in the hippocampus

closely tracks arousal states, but whether neurogenesis modulates the behavioral responses to changing arousal levels or influences the level of arousal produced by an event remains unclear. Due to their innervation by the sympathetic nervous system, fluctuations in pupil diameter provide a non-invasive readout of arousal states. However, pupillometry is typically performed under head-fixed conditions, limiting its utility in many behavioral tasks. Cardiovascular measures such as heart rate, heart rate variability, and blood pressure are also tightly regulated by sympathetic and parasympathetic control, providing insight into the state of autonomic nervous system activity. We are using surgically implanted radio telemetry transmitters in freely moving, male Long Evans rats to measure cardiovascular reactivity following elimination of adult neurogenesis. Neurogenesis is ablated by valganciclovir treatment in transgenic animals expressing the herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary acidic protein (GFAP) promoter, and unaffected by drug treatment in wild type (WT) littermates. We see no differences in heart rate, blood pressure, core temperature, or activity levels between WT and TK rats in the homecage. We are currently running experiments to compare cardiovascular arousal measures as rats undergo behavioral tests in which we observe effects of adult neurogenesis, specifically in tasks involving ambiguous or conflicting stimuli.

Disclosures: A. Swiercz: None. **H.A. Cameron:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

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Program #/Poster #: PSTR486.04/V22

Topic: H.08. Learning and Memory

Support: ZIAMH002784

Title: Investigating the role of adult hippocampal neurogenesis on positive learning experiences using puzzle toy learning in rats

Authors: M. A. GONZALEZ-PEDRAZA, M. C. TSUDA, ***H. CAMERON**;
NIH, Bethesda, MD

Abstract: Throughout adulthood, new neurons are continuously produced in the dentate gyrus (DG) of the hippocampus and eventually integrated into the hippocampal circuitry. We recently demonstrated that positive learning experiences in a rewarded spatial learning task, the flexible labyrinth maze, increases CA1 volume and novelty approach behaviors in normal rats, but not in rats lacking ABNs, even though both genotypes learned the task equally. The hippocampus is known for its importance for spatial learning; thus, it may be that spatial learning tasks have a unique ability to produce these changes. Alternatively, success in other forms of learning may have similar neurogenesis-dependent effects. Therefore, we wanted to ask whether other types of positive learning challenges produce similar behavioral and structural effects. To address this gap, we used transgenic rats expressing herpes virus thymidine kinase (TK) under a GFAP

promotor and suppressed adult neurogenesis with the antiviral drug valganciclovir. We presented wild-type (WT) and TK male rats with reward-oriented puzzle toys originally designed for cats and dogs and assessed the level of challenge each puzzle presented and whether ABNs impacted learning and/or performance in these puzzle tasks. Rats were first tested with a puzzle in which they had to slide knobs across a track to obtain a hidden food reward, with 8 possible rewards to earn in 5 min. Across 5 test sessions, both WT and TK rats equally completed this puzzle and earned all possible rewards. We then tested the same rats with a more challenging puzzle that required rats to lift lids and slide pieces left and right to obtain their reward, with a total of 16 available rewards. Even with this more challenging puzzle toy, both WT and TK rats earned similar number of rewards across 3 test sessions, suggesting no puzzle learning impairments in TK rats. As suppression of adult hippocampal neurogenesis did not grossly affect puzzle learning, we next plan to evaluate whether non-spatial puzzle learning experience positively affects hippocampal volume and novelty approach behaviors like the flexible labyrinth maze.

Disclosures: M.A. Gonzalez-Pedraza: None. **M.C. Tsuda:** None. **H. Cameron:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.05/V23

Topic: H.08. Learning and Memory

Support: NIH grant: ZIAMH002784

Title: Evaluating the role of adult hippocampal neurogenesis in empathy and prosocial behaviors in rats

Authors: *M. C. TSUDA, H. A. CAMERON;
NIMH, Bethesda, MD

Abstract: Prosocial behaviors, actions performed to benefit others, are observed in many species. Recent studies from other groups show that rats will help or console a distressed rat, demonstrating empathic helping. Brain regions reported to be involved in empathic helping include the sensory, anterior cingulate, orbitofrontal, and insular cortices, nucleus accumbens, lateral septum, hippocampus, and the habenula. The hippocampus plays a role in many social behaviors, including social memory/recognition, social affiliation, and social aggression, suggesting that it may affect prosocial behaviors as well. Neurogenesis continues throughout adulthood in discrete neuronal populations, one being the granule cells of the hippocampal dentate gyrus. These new neurons integrate in the hippocampal circuit and participate in hippocampal functions, including social behaviors such as aggression. We are investigating whether adult hippocampal neurogenesis plays a role in prosocial behaviors, specifically empathy-like behaviors, in rats using the helping behavior test. We completely suppressed adult neurogenesis in male rats transgenically expressing the herpes simplex virus thymidine kinase

(TK) under a GFAP promoter by treating them and wild type (WT) littermate control rats with the anti-viral drug valganciclovir. WT and TK rats were pair-housed with another WT rat and underwent 10 sessions of the helping behavior task, in which the rat learned to lift a door to free their cage mate from a clear acrylic box. Both WT and TK rats learned to release the trapped cage mate, showing similar latencies to open the door. We then increased the task difficulty by adding a barrel bolt sliding lock latch to the door to assess whether rats would persist in attempting to release their trapped cage mate. Interestingly, not only did more TK rats successfully open the latched door, but they were also faster in releasing their cage mate compared to WTs across 10 test sessions. Because WT and TK rats are equally capable of releasing their trapped cage mate from the box, we plan to further compare empathic behaviors toward different rats and door opening behavior towards non-social rewards and/or simultaneous presentation of social and non-social rewards. Lastly, additional studies will assess female WT and TK rats in the helping behavior test to understand whether adult-born neurons play a role in prosocial behaviors similarly in male and female rats.

Disclosures: M.C. Tsuda: None. **H.A. Cameron:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.06/V24

Topic: H.08. Learning and Memory

Support: ZIAMH002784

Title: Dorsal versus ventral silencing of adult-born granule cells in the hippocampus of rats

Authors: *N. FREEDGOOD[1,2], H. A. CAMERON[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Neuroscience, Brown University, Providence, RI

Abstract: The dentate gyrus (DG) of the hippocampus is one of few regions in the mammalian brain known to produce new neurons throughout adulthood. These new neurons contribute to various hippocampal-related processes, including difficult discriminations, cognitive flexibility, attention, motivation, and stress response. The dorsal and ventral regions have different extrinsic connectivity and are proposed to have different functions. The dorsal hippocampus is thought to play a crucial role in spatial navigation and memory, whereas the ventral hippocampus is thought to be involved in anxiety-like behaviors. It is expected that the adult neurogenesis that occurs at each pole of the DG might also have different behavioral functions. Few studies have tested these ideas, in part because it is difficult to target adult-born neurons in a spatially specific manner. We have tested a method to selectively silence new neurons in one portion of the DG using a Moloney murine leukemia retrovirus that expresses GFP and the chemogenetic receptor, hM4Di. Adult male rats bilaterally injected with virus in the dorsal or ventral DG were treated with clozapine-N-oxide (CNO) or saline 4 weeks later and exposed to a novel environment to

increase DG activity. Immediate early gene (c-Fos) expression was used to characterize the effects of silencing adult-born neurons on network activity. Cells co-expressing Fos and GFP were seen in the control animals but not the CNO treated animals, indicating that the virally transfected cells were effectively silenced. The densities of Fos+ cells in both the DG and directly downstream in the CA3 of the region targeted were significantly lower in the CNO treated animals compared to control animals. Future directions involve using this technique with established behavioral tasks to determine how spatially silencing or ablating adult-born neurons affects normal behavior.

Disclosures: N. Freedgood: None. **H.A. Cameron:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.07/V25

Topic: H.08. Learning and Memory

Support: NIH/NINDS R01NS115471

Title: Dentate Gyrus activity reorganization during a high cognitive demand pattern separation task

Authors: *C. C. M. CASTILLON[1], J. N. ARMSTRONG[1], A. CONTRACTOR[1,2,3];
[1]Neurosci., [2]Phychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL; [3]Neurobio., Northwestern Univ., Evanston, IL

Abstract: Activity in the dentate gyrus (DG) is critical to hippocampal function, orchestrating diverse cognitive processes such as pattern separation (PS) where the sparse firing of granule cells allows the separation of similar contexts. Within the neurogenic niche of the DG, adult-born granule cells (abDGCs) are continuously added to the circuit and have garnered attention for their potential contribution to hippocampal reorganization and memory flexibility. Accumulating evidence suggests that during a critical developmental window, abDGCs exhibit distinct functional properties, including enhanced excitability and synaptic plasticity. These unique cellular properties have been proposed to confer privileged roles on this population of neurons including engagement during behaviors that require discrimination of similar contexts. Notably, it has been proposed that abDGCs may modulate the local circuitry by contributing to the sparsity of granule cell activity through feedback inhibition. However, despite many years of study, dissociation of the precise involvement of abDGCs versus mature granule cells in DG function is still not fully clear. In this study, we employed tools to manipulate and measure patterns of activity of granule cells during an automated spatial discrimination task, varying the degree of spatial separation to change the cognitive demands of the task. Using TRAP2 mice for temporally defined labeling of active neurons, we found that both mature granule cells and young newborn neurons were increasingly engaged during tasks demanding high cognitive

effort, leading to the reorganization of the activity map within the DG. Furthermore, employing an inducible strategy for DREADD activity manipulation of abDGCs or mature neurons, we found that DREADD inhibition of young abDGCs modestly impacts performance while inhibition of mature granule neurons severely impairs task completion of most of the mice. In both cases, activity disruptions lead to a reorganization of the pattern of granule cell activity suggesting that the neural representation during the task are disrupted by these manipulations.Together, these findings reinforce the significance of neural activity in the DG in spatial pattern separation and highlight the contributions of both abDGCs and mature granule cells to behaviors requiring a high cognitive demand.

Disclosures: C.C.M. Castillon: None. **J.N. Armstrong:** None. **A. Contractor:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.08/V26

Topic: H.08. Learning and Memory

Support: CF-2023-I-796
PAPIIT-IA208524
AARF-21-722869

Title: H3k9me3 reduces neuron activation in the aged dentate gyrus

Authors: *G. PRIETO;
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Abstract: Recent evidence suggests that epigenetic mechanisms may contribute to memory deficits in aging. Specifically, in the hippocampus, the accumulation of the repressive epigenetic mark H3K9me3 (tri-methylated lysine 9 on histone H3) has been implicated in the silencing of genes essential for memory. Yet, the impact of the age-related increased H3K9me3 levels on neuronal function remains unclear. We hypothesized that H3K9me3 accumulation renders neurons refractory to stimulation. To assess the influence of H3K9me3 on neuronal activation, we reduced H3K9me3 levels by silencing SUV39H1, the major histone methyltransferase responsible for producing H3K9me3. SUV39H1 was knocked down by stereotaxic delivery of shRNA-containing adeno-associated virus (AAV) in the dorsal dentate gyrus. For stimulation, aged male mice (18 months old) were exposed to a novel environment for 15 min, and neuronal activation was assessed 1-hour later by measuring the presence of the Arc protein. Immunohistochemistry and flow cytometry data confirmed that SUV39H1 knockdown reduces H3K9me3 levels in transfected neurons (tagged with EGFP) compared to non-transfected ones. Notably, we observed increased levels (%) of activated neurons in the AAV-shRNA-SUV39H1 transfected population relative to control viral particles, suggesting an enhanced capacity for neuronal activation in response to the reduced levels of H3K9me3. These findings suggest that

the inhibition of SUV39H1 facilitates neuronal activation by decreasing the repressive H3K9me3 mark. Importantly, our data support the concept that epigenetic regulation through H3K9me3 plays a role in the decline of hippocampal-dependent memory with age.

Disclosures: G. Prieto: None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.09/V27

Topic: H.08. Learning and Memory

Support: NIH Grant U19NS104590
TACC Frontera Compute Allocation IBN22011

Title: Selectivity of granule cells in a computational model of the dentate gyrus

Authors: *I. RAIKOV[1], A. MILSTEIN[2], I. SOLTESZ[1];
[1]Stanford Univ., Stanford, CA; [2]Neurosci. and Cell Biol., Rutgers Univ., Piscataway, NJ

Abstract: The dentate gyrus (DG) is an integral part of the hippocampal formation that is thought to perform pattern separation of sensory inputs in order to facilitate context-specific encoding necessary for the formation and retrieval of memories. However, it remains largely unknown how the specific circuit, cellular and synaptic properties of DG contribute to the process by which the hippocampus transforms its entorhinal cortical (EC) inputs into place fields.
We present a computational supervised learning methodology to obtain biophysically realistic distributions of excitatory synaptic weights (structured weights) that lead to spatially-tuned neural activity of biophysical models of dentate granule cells (DGC) during simulated running on a linear track. Our proposed model is robust to heterogeneous combinations of spatial inputs of different field sizes, and reproduces spatial tuning patterns observed in the rat dentate gyrus. We have used this methodology to rapidly generate synaptic weight distributions for a large population of granule cells of a 1:1 scale, neuroanatomically- and biophysically-detailed computational model of the rat dentate gyrus, with multi-scale spatially-modulated inputs designed to mimic EC inputs, and we have used a parameter optimization strategy to determine synaptic conductance parameters that result in DGC place fields with signal-to-noise ratios similar to those observed experimentally.
Consistent with recent findings on dendritic integration, our model is predicated on the hypothesis that spatially distributed or asynchronous inputs are integrated linearly, whereas spatially and temporally correlated inputs induce dendritic nonlinearities via voltage-dependent NMDA receptor kinetics and short-term facilitation and depression, which in turn contribute to high signal-to-noise ratio in the somatic voltage response of the neuron. We show that without the non-linear amplification effect of NMDA short-term plasticity, structured synaptic weights

alone are not sufficient to generate somatic voltage depolarization that is consistent with experimentally observed DGC place fields.

Disclosures: I. Raikov: None. **A. Milstein:** None. **I. Soltesz:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.10/V28

Topic: H.08. Learning and Memory

Title: Molecular modulation of Planar Cell Polarity signaling modifies Pattern Separation and Completion processes in mice

Authors: *E. DANIEL[1,2,3], M. M. MOREAU[1,3], N. DEPRET[1,2,3], A. MARIGHETTO[1,3], M. E. MONTCOUQUIOL[1,3], N. A. SANS[1,2,3];
[1]INSERM U1215, Bordeaux Cedex, France; [2]University of Bordeaux, Bordeaux, France; [3]Neurocentre Magendie, Bordeaux, France

Abstract: Correct memory recall requires two cognitive processes. Pattern separation (PS) is an encoding process that enables the discrimination among similar experiences. Conversely, Pattern completion (PC) allows memory retrieval from partial or deleted information. In aging and Alzheimer's disease (AD), the balance between PS and PC is shifted in favor of PC over PS, inducing overgeneralization and overlapping memories. Mechanistically, PS and PC processes rely on the dentate gyrus (DG) and the CA3 hippocampal areas.
We previously showed that the *core* Planar Cell Polarity (PCP) protein Van Gogh-like 2 (Vangl2) is naturally enriched in the DG and the *stratum lucidum* of the CA3. A conditional knock-out in of *Vangl2* (*Vangl2*^{cKO}) in the DG improves the PS and impairs the PC in adult mice. At the molecular scale, deleting *Vangl2* results in a decreased phosphorylation of Vangl2 effectors, highlighting the disruption of the PCP signaling (Robert et al., 2020). Our goal is to use PCP-based molecular tools to modulate the PCP pathway to improve the PS and/or the PC in adult animals. Instead of disrupting the PCP signaling by using a *Vangl2*^{cKO}, we intend to overactivate or favor the PCP pathway over other signaling pathways (*e.g.* canonical Wnt signaling). We used two constructs based on Vangl2 effectors: Daam1 (CDaam1 truncation) and Dvl2 (Dvl2ΔDIX truncation). Using viral approaches, we overexpressed these constructs in the DG of adult mice, and used innovating and non-aversive behavioral tasks to assess the PS and the PC. Initial results in a touchscreen-based task show an improvement in PS with the CDaam1 construct, that were further validated in 8-arm radial maze. However, these DG-CDaam1 mice showed an impairment of the PC in the water maze paradigm. Preliminary data of the DG-Dvl2ΔDIX mice show no impairment of the PC in the Morris water maze test, but an improvement of the working memory in the Y-maze test. These results validate the CDaam1 construct as an effective tool that can modulate the balance between PS and PC, making PCP-based tools promising for preventing cognitive decline in the aging process and AD.

Disclosures: E. Daniel: None. **M.M. Moreau:** None. **N. Depret:** None. **A. Marighetto:** None. **M.E. Montcouquiol:** None. **N.A. Sans:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.11/V29

Topic: H.08. Learning and Memory

Support: NIH Grant R01MH131317

Title: Do olfactory stimuli affect dentate spikes?

Authors: *P. G. DEMETROVICH, J. R. TARANATH, L. L. COLGIN;
The Univ. of Texas at Austin, Austin, TX

Abstract: The dentate gyrus receives highly processed sensory information from the entorhinal cortices. Olfactory information specifically seems to have a specialized role in the rodent dentate gyrus. Individual granule cells have been shown to respond to individual odors (Woods et al., 2020), and certain odors elicit rhythmic bursts in the dentate local field potential (LFP) (Vanderwolf, 1992). Furthermore, input from the entorhinal cortices targeting the molecular layer of the dentate gyrus is thought to drive dentate spikes (DSs), which are irregular, short duration, large amplitude deflections in dentate LFP. Interestingly, DSs have been shown to enhance gamma rhythms within the hippocampus (Dvorak et al., 2021; Farrell et al., 2024), and the entorhinal cortices synchronize with the dentate gyrus at gamma frequencies during learning (Fernández-Ruiz et al, 2021). Therefore, DSs might play a role in generating dentate gamma for synchronization with entorhinal gamma. In this way, DSs could reflect instances of salient sensory information, perhaps olfactory information, flowing into the hippocampal circuit and switching it from an intraregional retrieval to interregional encoding mode. Under this theory, the sampling of salient odors would be predicted to (1) elicit DSs and (2) increase DS-associated gamma power within the dentate. To begin to test these hypotheses, we recorded LFPs from the dentate gyrus of freely moving rats (N=2) using either tetrodes or a Neuropixels probe during exploration of an environment in the presence and absence of salient odors. DSs were detected during active behavior, and spectrograms were computed on LFPs around the peak of each DS. Broadband gamma (25-100 Hz) power was averaged across these spectrograms, and a defined peak in gamma power was identified within 100 milliseconds of DSs. No clear differences were seen in DS-associated gamma power in the presence of salient odors. Taken together, these preliminary data and analyses replicate the finding of increased gamma power time-locked to DSs (Dvorak et al., 2021; Farrell et al., 2024) in rats but does not currently suggest that salient odors enhance DS-associated gamma power.

Disclosures: P.G. Demetrovich: None. **J.R. Taranath:** None. **L.L. Colgin:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.12/V30

Topic: H.08. Learning and Memory

Support: NINDS R56NS128177
NIA R01 AG76845

Title: Effects of aging and Alzheimer's disease on cue and place encoding in the mouse dentate gyrus

Authors: *E. SUN[1,2], A. HUROWITZ[1,2], R. HEN[1,2], C. LACEFIELD[1,2];
[1]Systems Neurosci., New York State Psychiatric Inst., New York, NY; [2]Psychiatry, Columbia University, New York, NY

Abstract: Background: The hippocampus and associated temporal lobe regions are implicated in episodic memory storage, and dysfunction in these areas is associated with disorders such as Alzheimer's Disease (AD) and age-related memory decline. The dentate gyrus (DG) is the initial stage of the hippocampal "trisynaptic circuit" and has been suggested to perform the computational role of pattern separation, or the disambiguation of similar input patterns to increase memory precision. Such functions may decline during aging and can be significantly impaired in individuals with age-related cognitive disorders.
It has been proposed that disruptions in entorhinal cortex input to the DG play a particularly important role in the cognitive alterations observed in aging and AD. The DG receives input from the lateral and medial entorhinal cortex, which have been suggested to encode egocentric information about sensory cues and allocentric spatial information respectively. While examining the activity of large populations of DG neurons using two photon (2P) calcium imaging in behaving mice, we have recently discovered that rather than integrating this information, the DG contains largely distinct populations of "cue cells" and "place cells". Here we examine properties of DG cue cells and place cells in mouse models of aging and AD, in order to see the effects of these manipulations on the stability and specificity of feature encoding in the DG over time.
Methods: We performed in vivo 2P calcium imaging in the dorsal DG of wild-type (WT), aged (18mo+) and APP/PS1 (AD) mice (n=4 each) during a spatial cue task. The mice ran on a 2-m-long treadmill while head-fixed, and a 2s odor cue was given in the middle of the track. This cue was shifted or omitted on a subset of laps in order to identify and determine the properties of DG cue cells and place cells. The activity of single neurons was subsequently followed over the course of one month to assess the stability of these representations. Responses to two similar odors were also measured to test stimulus selectivity.
Results: We found that aged/AD mice had stronger cue responses but less spatial modulation than WT mice, agreeing with our recent work on adult neurogenesis in the DG. Aged mice had similar average population stability as controls over short timescales, however AD mice showed larger defects in both stability and selectivity over time.
Conclusion: We examined systems-level encoding of sensory cues and spatial location by the

DG in both aged and AD mice and found both similarities and differences in properties of the DG network in these models, highlighting specific DG circuit alterations that occur during the normal aging process and AD.

Disclosures: E. Sun: None. **A. Hurowitz:** None. **R. Hen:** None. **C. Lacefield:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.13/V31

Topic: H.08. Learning and Memory

Support: NS064025

Title: Deciphering the role of NMDA receptor deficiency in dentate gyrus granule cells: implications for hippocampal pattern separation

Authors: *H. PANIKKAVEETTIL ASHRAF[1,2], J. I. WADICHE[3], L. S. OVERSTREET-WADICHE[3];
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Abstract: N-Methyl-D-aspartate (NMDA) receptors in dentate gyrus granule cells (DG GCs) are essential for a range of hippocampal functions, including synaptic integration, plasticity, pattern separation, and neurogenesis. Thus, NMDA receptors are involved in both excitatory neurotransmission and the regulation of granule cell survival and development. Previous studies have shown that genetic deletion of NMDA receptors in DG GCs impairs rapid in vivo pattern separation and contextual discrimination, resulting in reduced context-specific modulation of CA3 firing rates (McHugh et al., 2007). To understand how NMDA receptors can influence hippocampal information processing, we used in vitro whole-cell patch-clamp recordings of DG GCs in slices from adult mice to investigate the effect of acute pharmacological modulation of NMDA receptors on synaptically evoked firing rates and temporal pattern separation. Surprisingly, we found that either global NMDAR blockade (bath application of (R)-CPP) or block of NMDARs in a single GC (intracellular MK801) significantly increased DG GC mean firing rates in response to afferent stimulation of perforant path axons. Concurrently, real-time temporal pattern separation, quantified as a difference in similarity of output and input spike patterns (Madar et al., 2019), was reduced. These findings highlight the critical role of NMDA receptors in regulating both the firing rates and pattern decorrelation abilities of DG GCs and provide a potential cellular explanation for altered pattern separation following GC-specific NMDA receptor deletion.
References:
Madar AD, Ewell LA, Jones MV (2019) Temporal pattern separation in hippocampal neurons

through multiplexed neural codes. Plos Comput Biol 15:e1006932.
McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S (2007) Dentate Gyrus NMDA Receptors Mediate Rapid Pattern Separation in the Hippocampal Network. Science 317:94-99.

Disclosures: H. Panikkaveettil Ashraf: None. **J.I. Wadiche:** None. **L.S. Overstreet-Wadiche:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.14/V32

Topic: H.08. Learning and Memory

Support: NIH Grant R35 NS127219

Title: Theta burst stimulation of the perforant path increases bursting incidence in dentate gyrus granule cells

Authors: *C. ROSSMEISSL[1], M. B. JACKSON[2];
[1]Neurosci., Univ. of Wisconsin - Madison Neurosci. Training Program, Madison, WI;
[2]Neurosci., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Long-term potentiation (LTP) of synaptic transmission was first characterized in the dentate gyrus (DG) but its role in information processing remains unknown. Prior patch clamp studies of LTP have focused on changes in synaptic strength. These studies rarely focus on excitability and do not address questions about the impact of LTP on circuit function. Here we used hVoS, a genetically encoded optical voltage sensor to study LTP in the DG using Prox1-CreERT2 to target the sensor to intermediate progenitor GCs sparsely in newborn mice. hVoS experiments were then carried out on mature GCs in acute brain slices from 4-7 week-old mice. Recent work in our lab showed that GCs sporadically spike twice at brief intervals in response to stimulation with a single pulse. By facilitating synaptic output, these brief bursts have the potential to play a role in transmitting neuronal signals on to CA3 region through the putative DG information gate. The incidence of bursts increases when GABAA receptors are blocked. In this study, we found that theta burst stimulation (TBS) of the perforant path (PP) (in the presence of 5 mM GABAA receptor antagonist SR95531) induces a 62% increase in GC bursting incidence (paired t-test, p=3.41E-10, n=75 cells, 8 slices, 6 animals). In 20 trials prior to TBS, 29 of 75 GCs (38%) never spiked more than once. After TBS, 8 of these single-spiking GCs became bursters. The increased bursting of GCs following TBS will enhance the ability of these neurons to activate postsynaptic targets and transmit information through the trisynaptic circuit. Computational modeling is essential for integrating mechanistic discoveries into a comprehensive understanding of neuronal information processing. This finding will allow us to

test and improve biologically realistic computational DG models that aim to predict how neural circuits process sensory input, and how information is stored and retrieved during behavior.

Disclosures: C. Rossmeissl: None. **M.B. Jackson:** None.

Poster

PSTR486: Learning and Memory: Dentate Gyrus

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR486.15/V33

Topic: H.08. Learning and Memory

Title: A subpopulation of dentate gyrus somatostatin interneurons equipped with long term plasticity modulates memory discrimination

Authors: H. MA[1], ***J. LI**[2];
[1]Neurosci., Zhejiang Univ., New York, China; [2]Zhejiang Univ., Hangzhou, China

Abstract: Precise inhibition within the dentate gyrus (DG) is paramount for its optimal function. However, the heterogeneity among inhibitory neurons presents challenges in understanding and regulating their roles. Our investigation reveals that somatostatin (SST) interneurons, a prevalent type of inhibitory neuron in the DG, encompass two distinct subpopulations: one with local projections and the other projecting extensively to the medium septum, exhibiting divergent properties and functions. These functional disparities arise from differential expression of the pivotal molecule gCaMKII, which governs synaptic plasticity. Local SST interneurons exhibit high gCaMKII expression and possess long-term plasticity, while SST neurons projecting to the medial septum display low gCaMKII expression and lack long-term plasticity. The synaptic plasticity of local SST interneurons typically regulates theta oscillation and granule cell activity during mice's discrimination of similar contexts. Deleting gCaMKII in local SST interneurons abolishes their synaptic plasticity, impairing oscillation plasticity and memory discrimination without affecting mice's recognition memory. Taken together, our findings suggest that in the dentate gyrus, SST interneurons endowed with long-term plasticity modulate brain rhythms specifically during detailed memory discrimination, but not general recognition.

Disclosures: H. Ma: None. **J. Li:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.01/V34

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI 23KJ0330
JST MOONSHOT JPMJMS2012

Title: Modulation of cortico-muscular coupling during split-belt locomotor adaptation

Authors: *A. OSHIMA[1,2], H. YOKOYAMA[3], N. KANEKO[1], R. TAKAHASHI[1,2], K. TAKIYAMA[4], K. NAKAZAWA[1];
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Abstract: Humans can adjust their walking patterns in response to various environments. To date, a split-belt treadmill with two belts has been utilized to study locomotor adaptation. When healthy people are exposed to a perturbation that the walking speeds differ between right and left legs, their balance is disturbed and their walking patterns become asymmetrical, but several minutes later, their walking patterns become symmetrical. Such process of locomotor adaptation has been investigated from various perspectives, including kinematics, kinetics, as well as muscle and brain activities. However, it remains unclear whether a coupling between the oscillatory electrical activity of the sensorimotor region and that of the lower limb muscle changes associated with the split-belt locomotor adaption. Therefore, this study aimed to investigate the cortico-muscular coupling between the sensorimotor region and lower limb muscle during split-belt locomotor adaptation based on corticomuscular coherence (CMC). Nineteen healthy young males participated in this study. The experimental paradigm consisted of a baseline (0.9 m/s [5 min]), adaptation (right: 0.6 m/s, left: 1.2 m/s [15 min]), and washout (0.9 m/s [10 min]) periods. Each leg on the right and left side was defined as the "slow leg" and "fast leg," respectively. High-density electroencephalogram (EEG), surface electromyogram (EMG) of the tibialis anterior (TA) muscle, ground reaction forces, and motion-tracking data were recorded during the paradigm. Following preprocessing of the recorded EEG and EMG data, CMC between the cleaned EEG above the sensorimotor region and TA EMG was computed. We focused on CMC in the alpha (8-12 Hz) and beta (12-32 Hz) bands around heel contact (HC) and toe-off (TO) timings in each leg. CMC was then compared in the following five sub-periods: baseline, early adaptation, late adaptation, early washout, and late washout, using a linear mixed model. Aside from TO of the fast leg, CMC at both bands significantly decreased in early adaptation compared to baseline. Subsequently, CMC in the alpha band around HC of the slow leg and around TO of the fast leg showed a significant increase in late adaptation compared to early adaptation, but no other significant changes were observed in the adaptation period. These results revealed that when the perturbation is imposed, the cortico-muscular coupling between the sensorimotor region and TA muscle is disrupted. Throughout the adaptation period, the cortico-muscular coupling is enhanced in a leg- and gait phase-specific manner. These findings will advance our understanding of locomotor adaptation.

Disclosures: A. Oshima: None. **H. Yokoyama:** None. **N. Kaneko:** None. **R. Takahashi:** None. **K. Takiyama:** None. **K. Nakazawa:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.02/V35

Topic: H.10. Human Learning and Cognition

Title: Examining the Impact of Declarative Memory Practice on the Acquisition and Consolidation of Sensorimotor Adaptation

Authors: *M. P. MONTENEGRO[1], Y. LEI[2];
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Abstract: Humans possess both declarative and procedural memory systems. This study examined how declarative memory practice influences the acquisition and consolidation of procedural memory during sensorimotor adaptation tasks. In Experiment 1, participants first engaged in declarative memory practice using the California Verbal Learning Test before performing a motor adaptation task. In Experiment 2, the sequence was reversed: participants completed the motor adaptation task first, followed by declarative memory practice. Both experiments required participants to return four hours after initial training for a reassessment of their motor adaptation skills. The motor adaptation task consisted of a 45-degree visuomotor adaptation conducted on a desktop computer with a Wacom tablet setup. Preliminary findings from Experiment 1 indicated that declarative memory practice prior to the motor task did not improve skill acquisition. Conversely, Experiment 2 showed that performing declarative memory practice after the motor task significantly enhanced memory consolidation. These findings suggest that while declarative memory practice does not affect initial skill acquisition, it significantly impacts the consolidation of procedural memory during motor adaptation. Further research is necessary to explore the underlying neural mechanisms involved in the acquisition and consolidation phases of motor adaptation learning and the interaction between procedural and declarative memory systems.

Disclosures: M.P. Montenegro: None. **Y. Lei:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.03/V36

Topic: H.10. Human Learning and Cognition

Title: Testing the effect of two types of open-skills training on cognitive functions

Authors: *C. RUFFINO[1], S. GROSPRETRE[2];
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Abstract: Over the recent decades, the positive impact of physical activity on cognitive functions has been highlighted (1). However, the type of improvement could be highly dependent on the type of exercise. For instance, endurance-like activities and closed-skill sports appear less efficient than open-skilled activities. While closed-skill sports rely on optimizing one single movement within a standardized situation, open-skill activities are characterized by a variety of unpredicted situations that lead the practitioner to manage high adaptation skills. However, even if team sports are usually considered as open-skill sports by excellence, other booming activities, like parkour, offer an infinite variety of environment (2). Thus, the aim of the present study was two compared the effect of these two open-skill sports, indoor team sports (open-skills in the same environment) and parkour (open-skills in various environments), on cognitive functions. Forty healthy young participants (Age: 21.5 ± 3 years old) were split in two groups: team sports group (TS, n=19) and parkour group (PK, n=21). Both groups trained 4 weeks with 2 sessions of 2h per week, being composed of various activities including indoor collective ball games (e.g. volleyball, football) for TS and only parkour for PK. This latter involved practicing parkour focused on a wide variety of environments (one different per training session). Before and after training period, both groups were tested on a battery of cognitive tests: the trail making test (TMT), letter cancellation test (LCT), change blindness test (CB), visual memory test, instant and delayed recall of a list of 15 words for short- and long-term memory, respectively. The PK group significantly increased their score in both TMT and CB ($P < 0.001$), while the TS group did not ($P > 0.05$). Regarding the LCT and the working memory test (Instant recall of words), both groups increased similarly their performance ($P<0.001$). However, regarding long term memory, PK group remembered more words that TS group ($P<0.001$). Both training led to enhancement of working memory and selective attention (LCT). However, the variety of environments and the explorative approach of parkour to overcome a wide range of obstacles with various skills lead to a specific enhancement of observation capacity (CB test), long-term memory and visuo-spatial attention (TMT). Varying the configuration of environments seems to have a better effect on specific cognitive abilities, such as visual capacities, than practicing indoor team sports.
REFERENCES: 1. Chang et al. (2017), *J Sport Health Sci*, 6(1):89-95.2. Grosprêtre and Gabriel (2020), *Percept Mot Skills*, 128(1):96-114.

Disclosures: C. Ruffino: None. **S. Grospretre:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.04/V37

Topic: H.10. Human Learning and Cognition

Support: NIH Grant R01 NS132926 (S.D.M)

Title: Investigating structural learning in a de novo motor skill

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Abstract: It has been suggested that learning of new ("de novo") motor skills involves the creation of novel sensorimotor control policies. However, it is not known how abstract these new policies are during learning. This is a critical question, as the flexibility of new control policies, afforded by this abstraction, will dictate generalization of motor skills to new situations, and can shed light on underlying neural representations. While structural learning of abstract visuomotor mappings has been established in motor adaptation tasks, these data seem to be explained by participants using conscious cognitive reasoning strategies, which are likely not at play in more complex continuous control tasks. Thus, to address our main question, we had human participants perform a manual tracking task that required difficult, rapid continuous control of a cursor on a visual display under mirror-reversed conditions. We investigated whether or not "variable training", known to induce abstract structure learning, would improve generalization performance for a de novo motor skill. Participants performed a continuous cursor tracking task, where a cursor on a computer monitor moved along with the movement of their hand, which was occluded from view. During the training phase of the task, the cursor position was perturbed such that it was reflected away from the hand position with respect to an invisible mirroring axis. Critically, in the "fixed'' training condition, the orientation of the mirroring axis was set at the same angle during the entirety of the learning phase, whereas in the "variable" training condition, the mirror axis was positioned at various orientations, changing every 8 trials. Afterwards, participants in both conditions were presented with the same novel generalization test, where the cursor was reflected about a fixed mirror axis orientation that had not been observed during training. Our preliminary data show a significant effect of variable training on both learning and generalization. First, experiencing multiple orientations of mirror reversal throughout training induced faster learning. Moreover, variable training also induced better generalization, with participants in the variable condition showing improved transfer performance relative to the fixed condition when faced with a novel mirroring axis. These results demonstrate structural learning in de novo motor skills, suggesting that it is possible for the human motor system to efficiently learn and store novel, abstract mappings between perception and action.

Disclosures: S. Kang: None. **S.D. McDougle:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.05/V38

Topic: H.10. Human Learning and Cognition

Title: Unraveling the time-of-day influences on motor consolidation through the procedural-declarative memory conflict

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Abstract: The simultaneous involvement of procedural and declarative memory systems during motor learning leads to a conflict in motor consolidation. This results in weaker consolidation than when motor learning solely involves procedural memory[1]. Interestingly, disrupting this conflict with declarative interference, such as word list learning immediately after learning, enhances consolidation[2].Recently, we showed that motor consolidation (+ 24 hours) after training in a sequential finger-tapping task (SFTT) depends on the time-of-day at which training was scheduled. Precisely, we observed motor skill stabilization and improvement after afternoon and evening training, respectively, and deterioration after morning training[3]. We hypothesize that this difference is due to a conflict between procedural and declarative memory systems during motor learning in the morning but not in the afternoon.Sixty participants, divided into four groups, were trained on SFTT at 10 a.m. or 3 p.m. The training session was composed of 48 trials (6 sequences of 6 keys per trial). To evaluate motor performance improvement, we analyzed the skill (i.e., the ratio between duration and accuracy) of the first two and the last two trials. To evaluate motor memory consolidation, participants were retested in two trials 5 hours after the end of the training. To test the conflict between the two memories according to the time-of-day, two groups underwent declarative interference immediately after SFTT training, involving word list learning ($G10_{int}$, n = 15 and $G3_{int}$, n = 15), while the two other groups ($G10_{ctr}$, n = 15 and $G3_{ctr}$, n = 15) experienced no interference. We applied repeated measures ANOVA between groups on skill performances and one-way ANOVA on performance gains (i.e., the difference between tests) between groups. Following our previous study, the analysis revealed a deterioration of motor skill after morning training without interference ($C10_{ctr}$). However, the addition of a declarative interference ($G10_{int}$) significantly attenuated this decay, stabilizing motor skill. For afternoon training, motor skill stabilized for both groups ($G3_{ctr}$ and $G3_{int}$). Overall, these results suggest that the conflict between different memory systems seems to evolve according to the time-of-day, being stronger in the morning compared to the afternoon.
[1]Breton J, Robertson EM. (2014) *Trends Cogn Sci*. [2]Brown RM, Robertson EM. (2007) *Nat Neurosci*. [3]Truong C, Ruffino C, Gaveau J, White O, Hilt PM, Papaxanthis C. (2013) *NPJ Sci Learn*.

Disclosures: C. Truong: None. **C. Ruffino:** None. **C. Papaxanthis:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.06/W1

Topic: H.10. Human Learning and Cognition

Support: This research was supported by the Intramural Research Program of the NIH.

Title: Differential effects of age on skill memory formation, consolidation and forgetting

Authors: *W. HAYWARD[1], F. IWANE[2], E. R. BUCH[3], L. G. COHEN[4];
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Abstract: In young individuals, skill acquisition develops dynamically across multiple time scales ranging from seconds to days (Newell et al. 2001). Initial practice of a new skill results in prominent performance improvements (early learning) that develop over periods of practice (micro-online) and wakeful rest (micro-offline). Additional skill improvements emerge between practice sessions that include sleep (overnight consolidation). While age is thought to slow learning (Krampe 2002), its influence on various time scales of skill acquisition is incompletely understood. Here, we studied 344 healthy volunteers aged 21-70yo who learnt a novel motor sequence using a well-characterized typing task. Skill was calculated for five different age groups (21-30, 31-40, 41-50, 51-60 and 61-70yo). Early skill learning declined progressively across the five age groups. These skill gains were identified predominantly during rest rather than practice in all age groups. Interestingly, the proportion of micro-offline to micro-online learning was comparable across groups. Initial skill was not predictive of early learning across the lifespan. Day 1 end skill decreased with age. 235 participants completed a second practice day (Day 2) 20-30 hours later. Overnight consolidation decreased progressively across the different age groups. In the two youngest groups, Day 2 initial skill was preserved relative to Day 1 end skill. By contrast, skill memory declined (was forgotten) from Day 1 to Day 2 in the three older groups. Skill change between the first and second practice trials on Day 2 was comparable, suggestive of similar warm-up across ages. Day 2 practice led to larger skill acquisition in the older groups. Despite these gains, final end skill remained lower in older adults. We conclude that advancing age is accompanied by reduced early skill learning with comparable online and offline contributions, overnight forgetting and reduced consolidation.

Disclosures: W. Hayward: None. **F. Iwane:** None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

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Program #/Poster #: PSTR487.07/W2

Topic: H.10. Human Learning and Cognition

Support: K12HD093427
R25HD105583

Title: Behaviorally-relevant corticospinal plasticity is most strongly expressed during sensorimotor mu rhythm trough phases

Authors: T. SURESH[1], F. IWANE[2], M. ZHANG[3], M. MANESIYA[4], M. FREEDBERG[5], *S. HUSSAIN[4];
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Abstract: The human sensorimotor cortex plays a critical role in motor learning. Recent studies show that transcranial magnetic stimulation (TMS) applied to the primary motor cortex (M1) preferentially increases corticospinal output and improves motor learning when delivered during sensorimotor mu rhythm trough but not peak phases. Together, these studies suggest that the neurophysiological mechanisms (i.e., corticospinal plasticity) supporting motor learning may be most active during mu trough phases. If so, the magnitude of learning-related corticospinal plasticity should vary across mu rhythm phases. To address this possibility, we recruited healthy right-handed adults for a study involving TMS, EEG, EMG, and behavioral testing. Participants were randomly assigned to either a sequence or control group. Participants in the sequence group practiced the implicit serial reaction time task (SRTT), which contained an embedded, repeating 12-item sequence. Participants in the control group practiced a version of the SRTT that contained no such sequence. To evaluate learning-related changes in corticospinal output, we measured mu phase-independent and mu phase-dependent MEP amplitudes using real-time EEG-informed single-pulse M1 TMS (intensity=120% of RMT) before, immediately, and 30 minutes after the SRTT in both groups. To evaluate retention, both groups also performed a shorter version of the SRTT one hour after practice. Statistical analysis revealed that real-time targeting of mu peak and trough phases recorded over the left sensorimotor cortex was accurate in both groups. As expected, the sequence group showed greater sequence-specific learning than the control group during SRTT acquisition and retention. In both groups, mu phase-independent MEP amplitudes increased following SRTT acquisition but the magnitude of these increases did not differ between groups. In contrast, phase-dependent MEP amplitudes showed different patterns of increases between groups (GROUP X TIME X PHASE interaction; $p < 0.04$ for both timepoints). For the learning group, trough-specific MEPs increased more than peak-specific MEPs immediately after SRTT acquisition, while for the control group, trough-specific MEPs increased more than peak-specific MEPs 30 minutes after SRTT acquisition. Our results demonstrate that corticospinal plasticity induced by both motor sequence learning and movement repetition is biased towards sensorimotor mu rhythm trough phases, but at distinct time points. These findings are consistent with the presence of an endogenous, behaviorally-relevant phase-dependent plasticity mechanism within the human motor system.

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Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.08/W3

Topic: H.10. Human Learning and Cognition

Support: NINDS Intramural Research Program (IRP)

Title: Sequence action representations contextualize during rapid skill learning

Authors: D. DASH[1,2], F. IWANE[1], W. HAYWARD[1], M. BÖNSTRUP[1,3], E. R. BUCH[1], ***L. G. COHEN**[1];
[1]Human Cortical Physiol. and Neurorehabilitation Section, NINDS, Bethesda, MD; [2]Sonera, Inc., Berkeley, CA; [3]Department of Neurology, University of Leipzig Medical Center, Leipzig, Germany

Abstract: Activities of daily living rely on our ability to acquire new motor skills composed of precise action sequences. Early learning of a new sequential skill is characterized by steep performance improvements that develop predominantly during rest intervals interspersed with practice, a form of rapid consolidation. Recent fMRI and MEG studies have shown that prolonged practice over days and weeks induces changes in both sequence representations sets and in their individual action components [1, 2]. Less is known about changes in neural representations during rapid performance improvements that characterize early skill learning. Here, we asked if the millisecond level neural representation of an action performed at different contextual locations within a skill sequence differentiates or remains stable as learning evolves.We recorded magnetoencephalography (MEG) activity of 26 participants while they learned to perform a novel sequential motor skill task with their non-dominant left hand. We evaluated the neural representation for each finger movement by computing source space MEG activity time-locked to the onset of each finger movement. We evaluated the online (within-trial) and offline (between-trial) changes in the neural representation of the contextual actions (Index finger movement at ordinal position 1 and 5) for each trial. Next, we computed trial-by-trial differences in offline and online representations during early learning, evaluating their relationships with micro-offline gains (performance improvement during rest) and micro-online gains (performance improvement during practice), respectively.We found that the Euclidian distance between the neural representations of index finger movements performed at two different ordinal positions within the sequence increased progressively during both rest and practice periods of early learning before stabilizing. Representational differences were more prominent during rest than during practice periods ($t = 4.84$, $p < 0.001$) and strongly predicted micro-offline gains ($r = -0.84$, $R^2 = 0.7$, $p < 0.001$). We conclude that individual sequence action representations contextualize during early learning in parallel with skill gains. Further, the contextualized neural representation develops to a larger extent during rest than during practice intervals of early learning.
References: 1) Yokoi A & Diedrichsen J (2019) Neural Organization of Hierarchical Motor Sequence Representations in the Human Neocortex. Neuron. 2) Kornysheva K., et al. (2019) Neural Competitive Queuing of Ordinal Structure Underlies Skilled Sequential Action. Neuron.

Disclosures: D. Dash: None. **F. Iwane:** None. **W. Hayward:** None. **M. Bönstrup:** None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.09/W4

Topic: H.10. Human Learning and Cognition

Title: Computational modeling of contextual interference in motor learning

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Abstract: Motor learning and retention depend not only on the amount of practice, but also on the structure of practice. Blocked practice (BP) involves extensive repetition of the same task invoking a moderate level of challenge resulting in rapid performance gains but poor retention. In contrast, random practice (RP) involves frequent switching between to-be-learned skills which leads to a slow rate of skill acquisition but improved long-term retention and transfer, via a phenomenon known as contextual interference (CI). The features of CI resemble the “catastrophic forgetting” phenomenon observed in machine learning studies. Artificial neural networks (ANN) often experience poor retention and weak transfer to new tasks when tasks are learned in a blocked manner. This parallel suggests that CI arises from variations in neural representations shaped by the different practice structure, a commonality shared by both ANNs and the human brain. However, this commonality has not been systematically examined. We used a recurrent neural network (RNN), specifically an Elman network, implemented to simulate training of multiple sequential motor skills. We hypothesized that our RNN model would benefit more from RP manifest as improved retention and transfer, compared to BP. The network processes an input sequence consisting of seven elements, where each element specifies a particular motor output to execute. The network then sequentially generates seven motor outputs, each as a four-element binary array where a '1' represents execution of the corresponding motor option, and a '0' indicates no execution. To simulate the CI effect, we generated six unique input sequences, which were trained in both BP and RP formats. Two identical networks were pre-trained with ten arbitrary input sequences. One network was trained six generated input sequences in a blocked manner, and the other randomly. We ceased updates of the network weights and evaluated both models on the six input sequences utilized in training and a new set of 200 input sequences. Preliminary results from this model revealed all the robust signatures of the CI effect. Specifically, RP exhibited a slower decrease in performance error during training, resulting in slower skill acquisition compared to BP. RP displayed superior retention and transfer. This supports the idea that CI effects in motor learning can be attributed to the emergence of differential neural representations shaped by the practice structure, highlighting the relevance of our network model in elucidating behavioral phenomena and laying the groundwork for further understanding of how practice structure can influence motor memory development.

Disclosures: Y. Song: None. **T. Kim:** None.

Poster

PSTR487: Motor and Skill Learning

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.10/W5

Topic: H.10. Human Learning and Cognition

Title: Learning to modulate movement variability when making movements more precise

Authors: *J. WIJFFELS[1], R. RANGANATHAN[2];
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Abstract: Even though experts can produce seemingly consistent movements like a tennis serve, they still need the flexibility to change these movements depending on task requirements. Here, we examined the question of how precision constraints at different parts of the movement affect overall movement variability during learning. The optimal feedback control model of motor control predicts increased movement variability in 'task-irrelevant' dimensions to accomplish such higher precision - however, this model does not explicitly consider learning. Therefore, the goal of the study was to understand the effect on learning when increasing precision requirements on a trajectory. We designed a 2D via-point reaching task in virtual reality, where participants had to move between a set of targets along an S-shaped trajectory. We manipulated precision constraints of the trajectory at different points by modifying the sizes of the via-point targets. In addition, even though the task was in 2D, we recorded hand movement variability in the third 'task-irrelevant' dimension as well. Preliminary data suggest that with learning, participants tended to decrease variability at the points where precision was required by increasing variability at other parts of the movement. There was also increased variability in the third task-irrelevant' dimension. These results indicate support for the optimal feedback control model at least early in learning.

Disclosures: J. Wijffels: None. **R. Ranganathan:** None.

Poster

PSTR487: Motor and Skill Learning

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR487.11/W6

Topic: H.10. Human Learning and Cognition

Support: Australian Research Council Grant, DP200100234
Australian Research Council, FT230100656
Australian Research Council, DP180102383
Australian Research Council, FT220100294

Title: Effects of dopamine D2 receptor blockade on exercise-induced changes in excitation:inhibition balance and motor learning

Authors: *D. CURTIN[1], E. M. TAYLOR[1], J. J. HENDRIKSE[1], M. A. BELLGROVE[1], T. T. CHONG[1,2,3], J. P. COXON[1];
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Abstract: Exercise is known to benefit motor skill learning in health and neurological disease. Evidence from brain stimulation, genotyping, and Parkinson's disease studies converge to suggest that the dopamine D2 receptor, and shifts in the cortical excitation and inhibition (E:I) balance, are prime candidates for the drivers of exercise-enhanced motor learning. However, causal evidence using experimental pharmacological challenge is lacking. Here, we examined the effect of a selective dopamine D2 receptor antagonist, 800 mg sulpiride, on exercise-induced changes in cortical activity and motor skill acquisition. To test this, we measured exercise-induced changes in excitation and inhibition using paired-pulse transcranial magnetic stimulation (TMS) in 23 healthy female and male humans, and then had participants learn a novel motor skill — the sequential visual isometric pinch task (SVIPT). We examined the effect of D2 receptor blockade on these measures within a randomised, double-blind, placebo-controlled design. We had three main results. First, sulpiride abolished exercise-induced modulation of the cortical excitation:inhibition balance relative to placebo ($p < .001$, Cohen's $d = 1.76$). Second, sulpiride resulted in attenuated learning when acquiring the motor skill ($p = .005$, Cohen's $d = 1.36$). Third, motor skill acquisition was driven by an interaction between the D2 receptor and E:I balance. Specifically, poorer skill learning was related to an attenuated shift in the E:I balance in the sulpiride condition, whereas this interaction was not evident in placebo. Overall, our results demonstrate that exercise-primed motor skill acquisition is causally influenced by D2 receptor activity on motor cortical circuits. These findings have implications for how exercise should be prescribed in diseases of dopaminergic dysfunction

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Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.01/W7

Topic: H.13. Schizophrenia

Support: Medical Research Council Doctoral Training Programme (MRC DTP) Studentship
Pinsent-Darwin Scholarship

Title: A multi-paradigm approach to assess the role of precision-weighting of prior information in schizotypy

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Abstract: Predictive processing theory posits that perception and cognition depend on a combination of bottom-up and top-down information ('priors'). These inputs are precision-weighted and integrated in a method approximate to Bayesian inference to form and update a 'mental model' of the environment. While the use of priors can improve the speed and accuracy of processing, over-reliance can lead to inaccurate models and, in turn, phenomena such as illusions. Previous research has suggested that aberrant precision-weighting of priors may underlie delusions and hallucinations in psychosis and similar symptoms in the non-clinical population (schizotypy traits). However, results are inconsistent, with different studies reporting an under-reliance, over-reliance, or no significant difference regarding the reliance on priors in these populations. More recent work has claimed that contradictory results may reflect that priors can be defined based on their position in the cognitive hierarchy, although this remains largely theoretical, particularly as experiments usually only implement a single task (and thus a single type of prior). The present study investigates the role of precision-weighting of priors in schizotypy using a multi-paradigm approach designed to assess priors at different hierarchical levels. Seventy-three participants with no history of psychosis completed six computerised tasks testing participants' use of priors in language, memory, and visual and auditory perception. Data from each task were analysed to determine whether participants' reliance on priors related to schizotypy measures, including the schizotypal personality questionnaire (SPQ), Cardiff Anomalous Perceptions Scale (CAPS), and Peters et al. Delusion Inventory (PDI). Results revealed that, unlike some previous studies, individual differences in the precision-weighting of priors was only significantly related to schizotypy in two tasks. In a cloze probability task, participants with higher PDI scores displayed less reliance on priors, indicated by a reduced difference in reaction times between prior conditions. Elevated PDI scores were instead correlated with a greater reliance on priors in a task assessing detection of a near-threshold visual stimulus. This large dataset on multiple participants and paradigms contributes to addressing the mechanism underlying psychosis-like experiences in the general population. This approach also presents the opportunity to conduct further analyses on the factor structure underlying the precision-weighting of priors, which may (partially) explain previous contradictory results.

Disclosures: C. Miller-Silva: None. **F. Knolle:** None. **A. Greve:** None. **F. de Beer:** None. **T. Mujirishvili:** None. **J.R. Garrison:** None. **G.K. Murray:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.02/W8

Topic: H.13. Schizophrenia

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Title: A thalamocortical network readout for executive dysfunction in schizophrenia

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Abstract: Executive dysfunction is a prominent feature of schizophrenia and may drive core symptoms. Dorsolateral prefrontal cortex (dlPFC) deficits have been linked to schizophrenia executive dysfunction, but mechanistic details critical for treatment development remain unclear. Here we developed a human task predicted to engage dlPFC and its interactions with the mediodorsal (MD) thalamus based on prior animal work. We asked 17 healthy controls (HC) and 24 people with schizophrenia (SZ) to allocate attention to an upcoming auditory or visual target based on single trials where cueing uncertainty was parametrized. The SZ group showed higher sensitivity to cueing uncertainty than HC, indicated by a leftward psychometric shift ($U = 478$, $p = .004$). Task performance selectively correlated with right MD-dlPFC resting state functional connectivity (rMD-dlPFC; $F(1,15) = 6.531$, $p = .022$), which was independent of group, and specific to dlPFC. This suggested rMD-dlPFC resting state functional connectivity strength as predictor of conflict susceptibility of executive control. We directly tested this hypothesis in an independent cohort of 70 SZ patients that underwent working memory assessment, with and without a conflicting task (Screen for Cognitive Impairment in Psychiatry (SCIP) working memory task versus a Letter-Number Sequencing Working Memory (LNSWM) task). Indeed, rMD-dlPFC resting state functional connectivity positively correlated with the SCIP WM ($F(1,65) = 4.457$, $p = .039$) but not the LNSWM task scores ($F(1,65) = 0.661$, $p = .419$). To ask whether the rMD-dlPFC network directly engages in resolving conflict in executive function, we analyzed BOLD signals and brain-behavior correlation from a third dataset of 32 HC performing a probabilistic Go/NoGo reversal learning task. Following a rule reversal the right MD showed a significant BOLD signal (F, $x = 2$, $y = -14$, $z = 10$, $t(31) = 6.67$, $p < 0.05$). Using a

psychophysiology interaction (PPI) analysis with rMD as seed region, we found significantly enhanced rMD-dlPFC functional connectivity upon reversal (dlPFC, x = 42, y = 20, z = 26, t(31) = 4.37, p = 0.03), a neural measure that correlated with behavioral switching speed. Overall, our 3 independent experiments introduce and validate putative biomarkers for executive function in schizophrenia while highlighting animal circuit studies as inspiration for the development of clinically-relevant readouts.

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Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.03/W9

Topic: H.13. Schizophrenia

Title: Intracranial self-stimulation reversal learning facilitates superior colliculus-nitrergic system to mitigate mk801-induced cognitive inflexibility in rats

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Abstract: Intracranial self-stimulation reversal learning facilitates superior colliculus-nitrergic system to mitigate mk801-induced cognitive inflexibility in ratsAuthors:***A. M. Waghade*[1]*, S. N. Awathale*[2]*, N. K. Subhedar*[3]*, D. M. Kokare*[1]**1**Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj NagpurUniversity, Nagpur- 440 033, Maharashtra, India**2**Shri Vile Parle Kelavani Mandal's Institute of Pharmacy (SVKM IOP), Dhule 424001,Maharashtra, India**3**Indian Institute of Science Education and Research, Dr Homi Bhabha Road, Pune- 411008, Maharashtra, IndiaDisclosures:**A. M. Waghade:** None. S. N. Awathale: None. D. M. Kokare: None. N. K. Subhedar:None.***Abstract:***Schizophrenia is a devastating psychiatric disorder that disturbs cognitive functionsincluding declined cognitive flexibility. The midbrain superior colliculus (SC) regulatesvisual events and associates cognitive flexibility. The superficial grey layer (SuG) of SCis plentiful with neuronal nitric oxide synthase (nNOS; nitrergic system), which producesnitric oxide (NO) in the brain. The NO is associated with the pathogenesis ofschizophrenia. However, the impact of the SC-nitrergic system in the neurobiology ofschizophrenia is still elusive. The present study was designed to investigate the role ofthe SC-nitrergic system in MK801-induced cognitive deficits in rats. The fabricatedelectrodes were secured in the lateral hypothalamus-medial forebrain bundle (LH-MFB)for intracranial self-stimulation (ICSS). The ICSS reversal learning (RL) protocol wasemployed in the operant chamber for testing cognitive flexibility in rats. ICSS reversal-trained rats received MK801 (0.1

mg/kg; intraperitoneal) treatment, 15 minutes beforecognitive flexibility assessment, and the locomotor activity was assessed in an openfield test (OFT). A cFOS immunohistochemical (IHC) study was performed in SC. The7-nitroindazole (nNOS inhibitor; 7-NI) was administered in SuG. The nNOS IHC profileof SC in distinct groups was estimated. The DiI retrograde tracing was performed in SC.Herein, the MK801 group showed, declined correct lever pressings, increased switchingduration and cFOS IHC, and elevated locomotions in OFT than saline treated. The 7-NIshowed increased lever pressings and decreased switching duration, and the nNOS
IHC showed a significant elevation of nNOS cells in SC of ICSS reversal rats. Theretrograde study revealed the nitrergic signaling pathway from LH-MFB to SC. Thepresent study discovered that the ICSS-RL enables the SC-nitrergic system, SCefferent to the LH, and the manipulation of NO in SC has modulated the cognitiveflexibility in rats.

Disclosures: A.M. Waghade: None. **S.N. Awathale:** None. **N.K. Subhedar:** None. **D.M. Kokare:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Topic: H.13. Schizophrenia

Support: MH115188-01 NIH (NIMH)
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Title: Characterization of the behavioral phenotype of a YWHAE conditional knockout mouse model

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Abstract: The 14-3-3 protein family is composed of seven homologous isoforms: beta (β), gamma (γ), epsilon (ε), zeta (ζ), eta (η), theta (θ), and sigma (σ). Each of which is encoded by a unique gene: YWHAB (β), YWHAG (γ), YWHAE (ε), YWHAZ (ζ), YWHAH (η), YWHAQ (θ), and YWHAS (σ). 14-3-3 proteins are expressed abundantly in the brain and are involved in a variety of neuronal functions. Studies in both humans and animal models have implicated alterations of the 14-3-3 family in neurodevelopmental and psychiatric disorders, including schizophrenia. Previously, we have shown that functional inhibition of all seven 14-3-3 isoforms in the pyramidal neurons of the mouse forebrain via the transgenic expression of a dimeric 14-3-3 peptide inhibitor (difopein) results in schizophrenia-associated behavioral, molecular, and electrophysiological alterations. We have also observed a similar phenotype when using a CaMKIIα driven difopein virus to induce regional and cell-type specific functional inhibition of

14-3-3 in the glutamatergic neurons of the dorsal CA1 region of the hippocampus. In this study, we investigated the isoform specific role of 14-3-3ε in the forebrain glutamatergic neurons by crossing YWHAE floxed mice with CaMKIIα-Cre mice to create a YWHAE conditional knockout (CKO) model. Because 14-3-3ε plays a key role in neuronal development and glutamatergic signaling, we hypothesized that the loss of this specific isoform in forebrain glutamatergic neurons would be sufficient to induce schizophrenia-associated behavioral alterations. To characterize their behavioral phenotype, YWHAE CKO mice and their littermate controls underwent a battery of behavioral tests to evaluate their locomotion, memory, sociability, and sensory-motor gating. To assess for potential sex differences within our model, both males and females were included in all experimental groups. Based on the analysis of four cohorts of animals, YWHAE CKO mice do not significantly differ from controls in any of the behaviors tested. This suggests that the loss of 14-3-3ε in glutamatergic forebrain neurons is not sufficient to induce schizophrenia-associated behavioral alterations. However, a significant sex difference is apparent in several of the behavioral assessments. These results highlight the importance of including male and female subjects and performing sex-specific analyses in rodent models of schizophrenia.

Disclosures: M. Navarrete Mathews: None. **G.S. Lee:** None. **Y. Wu:** None. **Y. Zhou:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.05/W11

Topic: H.13. Schizophrenia

Title: The features of brain signals are associated with different levels of criminal responsibility in schizophrenia criminal defendants based on resting state EEG analysis

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Abstract: Introduction Previous studies indicated different psychiatric illnesses—such as schizophrenia, affective disorder, substance use and illness states may be associated with alterations in brain signals and behavior. We proposed that distinct brain signals features may be correlated with varying degrees of criminal responsibility among individuals with schizophrenia and aimed to analyze resting state EEG (rs-EEG) signals to identify potential brain features associated with different degrees of criminal responsibility. **Methods** 20 cases(closed eye periods in rs-EEG of criminal schizophrenia) with diminished responsibility or insanity (mean age: 38.8 ± 10.35, 83.3% male) and 18 cases with total responsibility (mean age: 43.83 ± 8.68, 80% male) were collected from databases in the Taoyuan Psychiatric Center, Taiwan. The first 5120 pre-processing data points would be adopted for further analyses—power spectrum density,

functional connectivity using Pearson correlation, and non-linear analysis: multiscale entropy (6 scales) for time series data to figure out the potential features of brain signals under different levels of criminal responsibility. A significance level of 0.05 was adopted for all analyses. Demographic variables such as age, sex, as well as the tendency of psychotic symptoms (anxiety, depression, paranoia) and cognitive function (IQ), were considered. Statistical methods, including tests for normal distribution, Chi-square, Fisher's exact test, independent two-sample T-test, and non-parametric analyses such as the Mann-Whitney U test, were employed as appropriate for examining these factors. **Results** According to the multiscale entropy analysis, no significant differences were observed across different scales of time series data in all channels. However, distinct trends emerged between the two groups: individuals with diminished responsibility or insanity exhibited higher brain complexity at higher scales (5-6 scale) and lower complexity at lower scales (1-2 scales). Notably, certain channels (F4, C4, and T4) displayed marginally significant differences between the two groups. Functional connectivity analysis showed distinct patterns between the two groups, including higher connectivity in certain channels (e.g., F4) and lower connectivity in others (e.g., C4). Regarding statistical findings, individuals with depressive tendencies exhibited elevated alpha wave activity (t=-2.136, *p=.048*), while no significant differences were observed in demographic data and symptoms. **Conclusions** The findings revealed alterations in physiological signals among individuals with diminished responsibility or insanity.

Disclosures: L. Lin: None. **A. Yang:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Title: The efficiency of functional network transmission during learning graph theoretic applications in schizophrenia

Authors: *C. ABEL II[1], D. BHATT[2], J. A. STANLEY[3], V. A. DIWADKAR[4];
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Abstract: Resting state fMRI signals have been summarized using graph theoretic analyses and revealed abnormal network organization in schizophrenia (SCZ)[1]. However, applications to

task-driven data are surprisingly rare, although fMRI signals are strongly task-driven [2]. Here, we applied graph theoretic analyses to fMRI data collected using an established learning task that recovers brain network dysfunction in SCZ [3]. We used the average shortest path length (ASPL) as a measure of integration [4] in a 246-node network (undirected graph)[5] for each of four conditions in the learning paradigm. fMRI data (Siemens Verio 3T) were collected while participants (n=88, SCZ=49, Ages: 18-45) completed an associative learning task [6]. All participants provided consent to participate. Each of eight task epochs were comprised of four conditions for Encoding, Post-Encoding Rest, Retrieval, Post-Retrieval Rest [7]. The full undirected functional connectivity (uFC) matrix (i.e. undirected graph) was estimated and normalized for each participant in each condition [8]. In each graph and for each participant, we computed the ASPL using Dijkstra's algorithm (Csardi and Nepusz, 2006). A shorter ASPL indicates greater network integration [9]. A two-way ANOVA (Group & Condition) revealed SCZ to have significantly higher ASPL regardless of condition ($F_{1,86}$ =10.96, p<.001, MSE = 0.187). Integration is central to network efficiency and analyses of rsfMRI show reductions in network integration in SCZ [10]. Yet global measures of network integration (such as ASPL) are rarely used to discover task-evoked changes in network integration in SCZ. Our results suggest that the functional connectome in SCZ during learning evinces less integration, *regardless* of task condition, contrasting with condition-specific effects observed using graph theoretic measures like Betweenness Centrality [11]. We suggest that global measures of network integration (such as ASPL) capture *generalized* features of a disintegration; by comparison condition-specific effects are more likely to be expressed in graph theoretic measures of node centrality [12].

1 doi.org/10.1002/hbm.25032
2 doi.org/10.3389/fnana.2016.00025
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5 doi.org/awn018/10.1093/brain/awn018
6 doi.org/10.1162/netn_a_00278
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8 doi.org/10.1126/science.1238411
9 doi.org/10.1016/j.neuroimage.2009.10.003
10 doi.org/10.1016/j.neuroimage.2017.03.051
11 doi.org/10.1089/brain.2016.0454
12 doi.org/10.1523/JNEUROSCI.2874-10.2010

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Poster

PSTR488: Computational Approaches to Neurocognition

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Title: The belief generalization across different decision granularities by abstracting beliefs onto the decision variable space

Authors: *H. LEE[1], J. LIM[2], S.-H. LEE[2];
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Abstract: Generalization is a hallmark of natural intelligence. Natural intelligence transfers knowledge acquired in a certain task to the other novel tasks by abstracting common structure between the tasks. Especially, in real world environments, it is crucial ability to utilize preceding experiences to adapt to future environment. Consequently, the choice of natural agents is not isolated from the history, which we call "history effect."
Here, we investigated how information is generalized in the lens of history effect. We will focus on the generalization across different "decision granularities." In contrast with conventional laboratory experiments, tasks in real world have various decision granularities. For example, if you are a fruit shop owner, you can display your apples in two grades ("small" and "large"), three grades ("small," "medium," "large") or finer granularity. In this situation, how your belief acquired in the two-grade situation can be seamlessly generalized to the three-grade situation? One possibility is that the generalization is implemented through the decision variable space (DV-space). Specifically, we hypothesized that the commitment to a categorical choice entails a commitment to the specific range on the DV-space. Furthermore, we hypothesized that this commitment to the range of the DV-space induces a prior belief of DV on that range. Critically, the width of the choice-induced prior on the DV-space gets narrower as decision is more granular. Therefore, as the granularity increases, the posterior of the DV-space on the next trial is more attracted toward previous prior, which implies that the more granular previous choice is, the stronger attractive bias of previous choice is.
To validate the implication, we conceived a new experiment paradigm in which decision granularity flexibly changes. In consistent with the implication, we found that the attractive bias gets stronger as granularity increases, which we will call the "granularity effect." Furthermore, when subjects directly reported the continuous estimate of DV or stimulus, we found that the continuous DV-estimate is also attracted toward previous choice more strongly as previous choice is more granular, whereas the continuous stimulus-estimate does not. Finally, by conducting a computational modeling, we confirmed that the granularity effect could be simulated by the generalization on the DV-space. Therefore, the results indicate that humans generalize knowledge across different decision granularities by abstracting beliefs onto the DV-space.

Disclosures: H. Lee: None. **J. Lim:** None. **S. Lee:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Topic: H.03. Decision Making

Support: NIH grant RF1DA055666

Title: Identifying behaviorally-relevant dimensions for causal validation of circuit mechanisms

Authors: *J. ZHANG[1], T. A. ENGEL[2];
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Abstract: Optogenetic technologies enable precise perturbations of neural circuits at the single-cell resolution, opening a possibility for testing circuit mechanisms of cognitive functions in behaving animals. Yet, generating predictions for such experiments has been challenging as complex, heterogeneous responses of cortical neurons obscure underlying circuit mechanisms. While high-dimensional recurrent neural networks (RNN) can fit neural responses, these models are generally underconstrained by data, which limits their interpretability and ability to predict perturbation outcomes. Therefore, the latent circuit model was developed to infer low-dimensional causal mechanisms from neural data [1]. The latent circuit model jointly fits neural responses and task behavior to identify a behaviorally-relevant subspace and a low-dimensional circuit model generating dynamics within this subspace. However, it is a priori unknown how many dimensions in the population activity are causally linked to task execution and how to choose the dimensionality of the latent circuit model to optimize its interpretability and predictive power.
We study these questions in RNNs trained to perform a delayed perceptual decision-making task. We fit RNN responses with latent circuit models of increasing sizes. For each size, we fit an ensemble of latent circuits with random initializations and quantify the similarity of the inferred latent connectivity across fits. We observe that the inferred connectivity varies across fit instances in smaller and larger models but becomes unique at some intermediate optimal circuit size. We find that connectivity in circuits with the optimal size correlates best with the latent low-rank connectivity structure that generates task-related dynamics in the RNN, while it deviates from this ground-truth structure in the smaller and larger circuits. We further test the inferred circuits via patterned perturbations in the RNN and find that latent circuits' predictive accuracy for behavioral effects in the RNN saturates at the optimal size. These results suggest that selecting the optimal model size based on uniqueness identifies latent circuits that can be reliably interpreted and accurately predict behavioral changes under targeted perturbations in the high dimensional system. Our work provides a theoretical foundation for inferring and causally testing circuit mechanisms in optogenetic perturbation experiments.
[1] Langdon & Engel. bioRxiv, 10.1101/2022.01.23.477431v1 (2022)

Disclosures: J. Zhang: None. **T.A. Engel:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.09/W15

Topic: H.03. Decision Making

Title: Dynamics of Decision-Making Process without Attractor Decision Points

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Abstract: Many theoretical studies hypothesize that the decision point in perceptual decision-making is an attractor. Although these theories effectively explain many aspects of experimental data, it leaves several questions unresolved: 1) Attractor theory predicts that delay between cue offset and decision point should not decrease decision accuracy, yet empirical studies suggest otherwise. 2) It is unclear how the dynamics reset from an attractor state to the baseline before next cues, because previous research primarily focused on the period from cue onset to decision point, while overlooked the inter-trial intervals. To overcome these limitations, we develop a machine learning model that reproduces the choice behavior of mice during a series of trials in our previous reported study (Wang et al., bioRxiv, 2024), and analyze the dynamics of the trained model. In our tone frequency discrimination task with head-fixed mice, tone category of low- or high-frequency alternated each trial with a transition probability of *p*. Mice biased the choices based on the tone frequency in the previous trial and the transition probability, indicating that mice used the experience of past trials to make choices. We used a continuous-time recurrent neural network (ctRNN) with Advantage-actor critic (Wang et al., *Nat Neurosci*, 2018) with a timestep of 10 ms to simulate the choices during the task. We reset the node activity of ctRNN after each episode (=100 trials). These settings allow the ctRNN to capture the dynamics of node activity both within and across trials. Our ctRNN successfully reproduced the choice behavior of mice and the activity of single neurons recorded from mice. To uncover the dynamics learned by our ctRNN model, we applied a numerical method for attractor analysis (Sussillo & Barak, *Neural Computation*, 2013). We set cue offset of each trial as the starting points and calculated the convergence points in the non-stimulus state. We observed convergence point attractors (convergence radius < 1e-3); however, these occurred significantly after the decision-making point. Even without forming attractors at decision points, our ctRNN model achieved 100% accuracy when noise was eliminated. To explore the reason behind this, we applied targeted dimensionality reduction (Mante et al., *Nature*, 2013) and projected model activity onto stimuli and choice axes. This revealed that while the stimuli axis decayed rapidly, the choice axis maintained information for a substantial period post-cue offset, retaining substantial information up to the decision point. Overall, we discovered an attractor-independent dynamics of decision-making, which can be experimentally validated.

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Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.10/W16

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Kilachand Fund Award

Title: A graph-theoretic approach to analyzing gaze data in a suite of abstract reasoning tasks

Authors: *Q. DO[1], L. BAKST[2], C. AHN[3], M. P. PASCALE[4], C. E. STERN[5], J. T. MCGUIRE[6], M. E. HASSELMO[7];
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Abstract: How can humans reason effectively and efficiently when facing a novel challenge? Several lines of work suggest that humans engage in a search process within a restricted hypothesis space to rapidly meet reasoning demands. However, directly investigating this process has proven challenging. Here we leveraged humans' propensity to explore the visual world to test the idea that gaze patterns reflect hypothesis search while problem-solving. In a pilot dataset (n=34), participants underwent eye tracking while attempting to solve 40 different reasoning tasks derived from an AI competition called the Abstraction and Reasoning Corpus. In each trial, participants inferred a hidden rule from 3 examples and applied the rule to a novel puzzle by drawing the solutions on an interactive web interface. They also provided confidence ratings for their solutions before receiving feedback. If gaze patterns reflect a hypothesis search process, the complexity of the pattern should be associated with participant confidence, as well as accuracy – the search process would likely be more challenging for tasks in which confidence is low, and this should relate to the empirical difficulty of the task itself. Gaze traces from the interval in which participants examined the task interface prior to providing their solution were decomposed into fixations and saccades, and represented as a directed graph, with fixations as nodes and saccades as edges. We then fit a Nested Stochastic Block model to the graphs for each participant and task. We found that the minimum description length over the nodes and edges of the gaze model is negatively correlated with the individual's confidence rating for each task (Pearson's $r=-0.71$, $p<0.001$), along with their accuracy ($r=-0.60$, $p<0.001$). The average number of nested structures returned by the model is also negatively correlated with the average confidence rating ($r=-0.65$, $p<0.001$) and accuracy ($r=-0.50$, $p<0.001$). This supports the idea that difficult tasks (with lower confidence and accuracy) might induce more complex hierarchical structures in the gaze patterns, reflecting a more involved search process. We also constructed graphs in which nodes are fixations on different areas of interest, and edges are saccades connecting these areas. Using the PageRank algorithm to rank nodes, we found that success in

the task was associated with more fixations to the third example provided in the task (r=0.64, p<0.001), further suggesting that gaze predicts problem-solving outcomes. This lays the foundation for additional examination of the idea that gaze reflects hypothesis search and might reveal the features and preferences driving this process.

Disclosures: Q. Do: None. **L. Bakst:** None. **C. Ahn:** None. **M.P. Pascale:** None. **C.E. Stern:** None. **J.T. McGuire:** None. **M.E. Hasselmo:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.11/W17

Topic: H.03. Decision Making

Support: NSTC 110-2410-H-A49A-504-MY3
NSTC 111-2628-H-A49 -004 -MY4

Title: Learning heavy-tail and non-heavy-tail return distributions in a financial decision task

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Abstract: Recent studies suggest that dopamine neurons in the ventral tegmental area implement distributional reinforcement learning (RL) where these neurons convey information about reward distributions. However, it remains unclear whether humans implement distributional RL and use information about reward distributions when making decisions. In this study, human subjects participated in a financial investment task where they faced two financial portfolios that differed in their log-return distributions. One distribution was a Laplace distribution, which we picked to mimic the heavy-tail nature of return distributions in certain financial markets, most notably the stock markets. The other distribution was a uniform distribution (non-heavy-tail). The two distributions had the same mean and variance so that any difference in choice behavior between the two distributions cannot be attributed to the mean and variance statistics. Both distributions spanned positive and negative returns. Participants encountered each distribution in two consecutive blocks of trials (n=80 per distribution), with order randomized across subjects. On each trial, information about the log-return of the portfolio was randomly drawn from the corresponding distribution where return is defined by the ratio of the current value (V_t) and the previous value (V_{t-1}) . Hence, the task was Markov in nature. At the beginning of the experiment, participants were endowed with the portfolios. Each trial consisted of two phases, a prediction phase followed by a decision phase. In the prediction phase, participants were asked to predict whether the portfolio value would go up or down. If participants made the correct prediction, they were subsequently asked to estimate the probability that simple return $(V_t-V_{t-1})/V_{t-1}$ would exceed certain threshold (0.01, 0.05, 0.1, 0.15). After the prediction phase, information about the current value was revealed and subjects had to decide whether to buy or sell the portfolio. Once

in every 10 trials, we also asked subjects to predict portfolio value 10 trials from now and the lowest value during the next 10 trials. Preliminary results (6 subjects) suggested that participants showed different patterns of portfolio predictions between the Laplace and uniform distributions. Two out of 6 participants showed different buy/sell strategies between distributions. Together, these results suggested the possibility that, under relatively small sample size, people can discriminate heavy-tail from non-heavy-tail distributions, which further impacts their decision-making.

Disclosures: Y. Huang: None. **S. Wu:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.12/W18

Topic: H.03. Decision Making

Title: Control and Agency in Human-AI Collaboration

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Abstract: Control and Agency in Human-AI Collaboration Our lives are becoming increasingly integrated with artificial intelligence (AI) systems, ranging from self-driving vehicles to large language models. Integration of AI raises critical questions about our sense of agency (SOA) — the subjective feeling of control over one's actions and their consequences. Specifically, AI integration may have a significant impact when our decisions and actions are supported by AI. This study aimed to investigate how different types of AI engagement influence human SOA and decision confidence. To this end, we designed the Effort-Expenditure for Rewards Task with three blocks where AI can assist with 1) the “decision” of a course of action, 2) the “execution” of an action. In block 1, participants chose between two options varying in the level of physical effort to obtain monetary rewards: a “high effort” (i.e., 100 button presses using their non-dominant pinky in 21 secs) and an “low effort” option (i.e., 30 button presses using their dominant index finger in 7 secs) (*decision phase*). The high effort was always associated with larger reward. After decision phase, participants performed button presses which raised a virtual bar until reaching the top to obtain the reward (*execution phase*). Block 1 served as a baseline. In block 2 participants made the choice between the two options, but an AI was engaged during execution phase. Unbeknownst to the participants, an AI helped or impaired participant’s execution (some trials without any AI). In block 3, AI was engaged in the decision phase and made the choice, but participants themselves performed the execution. On each trial, we measured participant’s confidence about winning and their SOA about performance. For blocks 2 and 3, we also measured participant’s evaluation of the AI. Preliminary results indicate that the integration of AI alters human SOA, with the degree of impact varying according to the AI

engagement. Compared to block 1, SOA was dropped in blocks 2 and 3, which was modulated by the outcome (success or failure) and effort (high vs. low). In Block 2, where AI was engaged in execution phase, the AI's helping of performance generally preserved or slightly improved SOA for the high but not for low effort. In contrast, AI's impairing of performance led to a marked reduction in SOA overall. In block 3 (AI in decision phase), participants reported lower SOA for both high and low effort. These findings collectively demonstrate that AI's role, whether in decision or execution, critically modulates SOA. The reduction in SOA is influenced by both the effort and the outcome, underscoring the complex dynamics between human autonomy and AI assistance.

Disclosures: R. Mohammadsadegh: None. **Y. Kwak:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.13/Web Only

Topic: H.03. Decision Making

Support: FJNU Research Start-Up Funds

Title: Predicting metacognitive decision-making in rats: A behavioral and computational analysis in a modified Skinner Box

Authors: Y.-X. WANG, C.-Y. LIU, J. RAO, *B. YIN;
Sch. of Psychology, Fujian Normal Univ., Fuzhou, China

Abstract: Metacognition plays a critical role in decision-making during learning, yet its regulatory mechanisms remain insufficiently understood. This study utilizes an animal model with rats in a modified Skinner box to explore metacognitive decision-making in tasks of varying difficulty and reward ratios. We aimed to assess their metacognitive abilities through behavioral analysis and computational modeling, specifically focusing on decline rates, correctness rates, and reaction times across trials. In Experiment 1, rats showed higher correctness rates and faster reaction times in optional trials than in forced lever trials, where they had to differentiate between short (2s) and long (8s) sound stimuli. Experiment 2 revealed a decline in correctness rates with increasing stimulus difficulty, but no significant difference in correctness rates between trial types. Decline rates remained stable across difficulties. Experiment 3 demonstrated that reward ratios significantly influenced rats' decisions to decline. Subjects with low decline rates exhibited shorter reaction times, while high decline rates were associated with longer reaction times despite increased lever rewards. For computational modeling, we employed the Bayesian Information Criterion to select a mixed-effects model and also implemented artificial neural network models within a meta-learning framework. Mixed-effects modeling showed that trial type had a significant impact on reaction times and correctness rates. Optional trials led to faster responses and higher correctness rates compared to forced lever trials, while forced sensor

trials had the longest reaction times. Stimulus difficulty significantly affected correctness rates, which declined as difficulty increased. The 1:2 reward ratio group had a significantly higher decline rate that increased with stimulus difficulty. Meta-learning models that incorporated both contextual cues and individual traits, such as tendencies to give up, predicted decision-making behavior with up to 78% accuracy. These models effectively mirrored the overall rate of task giving up and correct lever selections by rats, indicating the model's accuracy in predicting their metacognitive decision-making behavior.

Disclosures: Y. Wang: None. **C. Liu:** None. **J. Rao:** None. **B. Yin:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.14/W19

Topic: H.03. Decision Making

Title: Defining the optimal form for subjective value encoding by the brain, a numerical approach

Authors: *S. SINHA[1], A. TYMULA[3], P. W. GLIMCHER[2];
[1]New York Univ., New York City, NY; [2]New York Univ., New York, NY; [3]Univ. of Sydney, Sydney, Australia

Abstract: How should value be best represented in the brain? Early studies of value encoding in the brain hypothesized that internal representations of the value of an option or action should be represented at the linear or logarithmic transform of objective value. Recording studies in monkeys, however, showed sigmoidal functions sensitive to features of the environmental distribution of rewards. Building on efficient coding theory, our groups have argued for a divisive normalization-style representation, noting that it is optimal for a particular class of environmental reward distributions (Pareto III).
All of these prior studies use empirical measurements of the reward encoding function to make guesses about efficiency. In this project, we invert that logic. Here we specifically define the objective of the nervous system to be the maximization of long-run reward rates. We then use a mixture of analytical and numerical methods to answer the question: What specific encoding function is reward maximizing? (In a parallel investigation we explore error-minimizing functions.)
Our numerical analysis reveals that in order to answer this question, an efficient chooser must have a specified encoding noise level. We find that for a perfect encoder (more precisely we find that as noise goes to zero in the limit) a linear encoding function is always optimal. Sigmoidal and curved functions emerge only as the encoding noise (or more formally the inverse capacity) becomes significant. As the noise grows, we find that the precise reward-maximizing encoding function depends critically on the reward structure of the environment. To define an optimal encoder at any given (non-zero) noise level one must know the distribution of rewards in the

environment and the number of options drawn from that environment that the nervous system faces.
When analyzed this way, we find that the sigmoidal encoding functions mirroring the value function of Kahneman and Tversky are optimal for mid-noise systems facing uniformly distributed rewards. In contrast, logarithmic encoding functions are optimal for exponentially distributed reward environments like the one studied by Bernoulli. Notably, our research unveils a striking resemblance between the derived and the biological utility functions observed in the brain, hinting at potential optimality under specific constraints. This correlation opens avenues for further exploration and validation, presenting an exciting prospect for understanding the fundamental mechanisms driving human choice behavior.

Disclosures: S. Sinha: None. **A. Tymula:** None. **P.W. Glimcher:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.15/W20

Topic: H.03. Decision Making

Support: NIH ZIA-MH002983

Title: Discrete performance states in choice behavior of rats during an odor-guided reward learning task

Authors: *E. DADBHAWALA[1], S. ZOROWITZ[1], Y. K. TAKAHASHI[2], M. R. ROESCH[3], G. SCHOENBAUM[2], A. LANGDON[1];
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Abstract: Choice behavior on reward-guided learning tasks is shaped by trial-by-trial experience with outcomes. However, choices are also potentially modulated by slower fluctuations in internal behavioral state related to engagement, choice strategy, and/or motivation. Here, we analyzed the choice behavior of rats as they performed an odor-guided reward learning task, to test for the influence of discrete “performance states” maintained across sequences of trials. In this task, rats could respond to an odor cue by choosing one of two reward wells; two odor cues were ‘forced’ to the left or right well, leading to reward only on that side, while one odor was ‘free’ choice with both the left and right well leading to reward. In each block, one well had either a shorter delay to reward or a larger reward amount, and reward contingencies were switched between blocks to engage within-session learning over trials. We analyzed choice behavior (N=11; each with 10 or more sessions) using a state-switching logistic regression model (a GLM-HMM) to test whether discrete performance states could be isolated from choice sequences across each session. In this model, a finite set of hidden Markov states are each associated with a different linear weighting on influences of choice, expressed as a GLM. We

used an expectation-maximization (EM) procedure to fit a set of k-state GLM-HMMs for k in {1, 6} to choice data using previous reward outcomes, previous choices and side bias as regressors for the linear model. We assessed model performance using 4-fold cross-validation for fitting across all subjects, and leave-one-session-out cross-validation for fitting to individual rats. Model comparison revealed that the choice data of each rat was significantly better explained by a 3-state GLM-HMM compared to a reference 1-state GLM (difference in mean test log-likelihood: 0.026 bits/trial, SE = 0.002). This means a test dataset of 250 choice trials (session average is 280) is 100x more likely to have been generated by the 3-state than the 1-state model. Model weights for each state indicate choice is governed by discrete optimal and sub-optimal performance states, where optimal states are characterized by high sensitivity to reward outcomes and minimal side bias, and sub-optimal states are characterized by lower sensitivity to reward outcomes and higher side bias. Fit transition probabilities between performance states indicate they persist trial-to-trial, with infrequent transitions. These results provide evidence for evolving biases in choice strategy of rats that correspond to discrete performance modes within a session of this task.

Disclosures: E. Dadbhawala: None. **S. Zorowitz:** None. **Y.K. Takahashi:** None. **M.R. Roesch:** None. **G. Schoenbaum:** None. **A. Langdon:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.16/W21

Topic: H.03. Decision Making

Support: Simons Collaboration on the Global Brain Pilot Award
NIH

Title: Inter-regional neural dynamics underlying self-paced action decisions

Authors: *M. ELBAZ[1], K. BUTTERER[1], J. I. GLASER[2], A. MIRI[1];
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Abstract: Sixty years after the discovery of a slow monotonic drift in electroencephalographic recordings preceding voluntary self-paced actions (“the readiness potential”), its physiological underpinnings remain elusive. A classical interpretation holds that readiness potential onset reflects the decision to act, with the drift thereafter proceeding deterministically to movement onset. However, more recent analyses suggest that the readiness potential’s monotonicity may be an artifact of trial averaging; rather than a slow, deterministic process, fast stochastic processes underlie self-paced decisions. In the absence of measurements resolving neural dynamics during single trials, these competing accounts have persisted. We have taken a comparative behavioral approach to address this, training mice to initiate an action in two contexts: in response to cues (instructed) and in their absence (self-paced). We can thus identify neuronal dynamics specific to

self-paced decisions that are not motor-related. We used Neuropixels to simultaneously record activity in several brain regions implicated in self-paced decisions. The activity preceding movement enables above-chance classification of decision-making contexts. We parcellated this preparatory activity into subspaces shared between decision contexts or unique to self-paced decisions. Above-chance classification remains possible within both subspaces. These results imply that decision-making contexts differ through distinct temporal profiles within shared subspaces, and through activity modes specific to self-paced decisions. Finally, projecting single trial activity onto either subspace allows prediction of subsequent movement initiation. Preliminary results show that prediction accuracy improves closer to movement onset, in line with stochastic models. Collectively, our work helps arbitrate between models underlying the neural basis of self-paced action decisions.

Disclosures: M. Elbaz: None. **K. Butterer:** None. **J.I. Glaser:** None. **A. Miri:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.17/W22

Topic: H.03. Decision Making

Support: CONAHCYT 772680
CONAHCYT Paradigmas de la Ciencia de Frontera: 319212
PAPIIT BG200521

Title: Perceptual discrimination of temporal patterns in humans and monkeys

Authors: *M. ESPINOZA, K. MERCADO, V. DE LAFUENTE;
Inst. de Neurobiologia, Queretaro, Mexico

Abstract: The motor system executes and controls complex movement sequences with tight temporal constraints, such as those observed in dance, speech, and music production. However, less is known about the role of the motor system in perceptual and behavioral contexts that do not require immediate movement execution. The internal brain simulations that arise from learning the temporal structure of sensory events might be a mechanism by which the motor system influences the perception of rhythm and time. To explore this, we asked humans (n=15) and monkeys (n=2) to discriminate trains of brief sensory pulses separated by either constant or variable inter-pulse intervals. Importantly, subjects were free to determine the stimulus observation time. The behavioral results are consistent with the proposal that humans and monkeys discriminate regular from irregular temporal patterns by accumulating sensory prediction errors over time. We observed that humans seem to follow an accumulation-to-bound strategy in which the sum of prediction errors triggers the choice and response time. Monkeys, however, seem to incorporate a deadline over the total elapsed time to determine their choice.

Thus, our results suggest that humans and monkeys discriminate temporal patterns by implementing different speed-accuracy tradeoff strategies.

Disclosures: M. Espinoza: None. **K. Mercado:** None. **V. de Lafuente:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.18/W23

Topic: H.03. Decision Making

Support: NIH R01 DC017797
NIH R01 NS115233
NSF IGERT 1250104
Financial support from the Dunn Foundation

Title: Mice use hierarchical Bayesian inference to model uncertainty when foraging in stochastic environments

Authors: *J. WEBB[1], P. STEFFAN[1], B. Y. HAYDEN[1], D. LEE[2], C. KEMERE[3,1], M. J. MCGINLEY[1,4,3];
[1]Baylor Col. of Med., Houston, TX; [2]Johns Hopkins Univ., Baltimore, MD; [3]Rice Univ., Houston, TX; [4]Jan and Dan Duncan Neurolog. Res. Inst., Texas Children's Hosp., Houston, TX

Abstract: In natural environments, animals must make informed choices regarding nutrition, shelter, or predation. One ubiquitous task across species, and consequently impactful in shaping the evolution of neural circuitry related to decision-making, is patch-based foraging. In patch-based foraging, animals must harvest resources that are finite and aggregated in confined geographical areas, called patches, by processing information about the rate of intake, the cost of traveling to the next patch, and, importantly, the uncertainty inherent in natural settings. The optimal strategy in the absence of uncertainty, termed the marginal value theorem (MVT), has been well-demonstrated in many ethological studies, but naturalistic patch-based foraging with uncertainty has been difficult to model in an experimental setting. Here, we developed a patch-based foraging task for freely moving and head-fixed mice in order to investigate decision-making in the face of multiple layers of uncertainty. Briefly, the mice ran on a physical or virtual track until they arrived at a patch, at which point they could lick for fixed-volume sucrose solution rewards. The timing of rewards followed a modified inhomogeneous Poisson process to mimic both patch depletion and natural stochasticity. At any time, mice could leave the patch (residence time) and travel to the next, replenished patch, which began dispensing rewards at the same initial Poisson rate in response to licking. Meanwhile, auditory cues provided information about the patch location and availability of rewards. In both freely moving and head-fixed experiments, MVT-based models outperformed heuristic strategies (such as leaving after a fixed number of rewards or elapsed time without a reward), suggesting that our experimental

paradigms replicated naturalistic patch-based foraging. In freely moving environments with highly stochastic rewards, MVT-based models of residence times failed to account for the multiple layers of uncertainty. Rather, a hierarchical Bayesian model of the reward rate best explained foraging behavior by allowing prior probabilities of the environment to be influenced by recent observations. In the best performing model, priors displayed moderate uncertainty about environmental parameters, and the likelihood incorporated reward times from only the current patch. Taken together, our results suggest that mice handled the multi-layered uncertainty, or meta-uncertainty, pervasive in naturalistic settings, by independently modeling its sources. This hierarchical model has important implications for the study of neural circuits underlying decision-making processes.

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Poster

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Topic: H.03. Decision Making

Support: K01MH108815
UL1 TR001860
TL1 TR001861
NSF 2319580
NSF NRT 2152260

Title: Temporal Convolutional Neural Networks Reveal Neural Mechanisms Underlying Deliberation

Authors: *K. MOXON[1], A. MOGHBEL[2], J. A. OVERTON[3], I. SAEZ[4], L. PETERS[5]; [1]Univ. of California Davis, Davis, CA; [2]Univ. Of California Davis Neurosci. Grad. Program, Davis, CA; [3]Neurolog. Surgery, UC Davis, Ctr. for Neurosci., Woodland, CA; [4]Mount Sinai, New York, NY; [5]Computer Sci., Univ. Of California Davis, Davis, CA

Abstract: During decision-making, when there are a small, finite number of choices, people generally consider one and then the another option, building knowledge based on past experience and any new information until they make their decision. Abnormalities in decision-making have been implicated in a variety of cognitive disorders and developing better treatments for these disorders necessitates a better understanding of the neural underpinnings of decision-making in humans. Our study built a temporal convolutional neural network model using changes in high gamma power as the input features. High gamma power was extracted from local field potentials recorded across multiple brain regions from intracranial electrodes in human subjects undergoing Phase 2 clinical assessment of their seizures. We show that 1) the final choice can be accurately

predicted on a single-trial basis, 2) the frequency of transitioning between options during deliberation is coherent with the on-going delta band activity and 3) choice is time-locked to the phase of the delta. Thess data suggest that neural computations underlying single trial decision-making behavior involve switching between neural representations of each option and knowledge accumulation toward a final decision. Moreover, these computations utilize similar neural dynamics. These findings identify neural dynamics of deliberation that are consistent with behavioral accounts of decision making and offer a potential pathway towards neuromodulatory treatments for psychiatric disorders.

Disclosures: K. Moxon: None. **A. Moghbel:** None. **J.A. Overton:** None. **I. Saez:** None. **L. Peters:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.20/W25

Topic: H.03. Decision Making

Support: NIMH Grant K01MH108815
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NSF Grant 2319580
NSF Grant 2152260

Title: Linear Dynamical Systems Modeling of Intracranial EEG During Choice

Authors: *A. ROADARMEL[1], L. PETERS[2], J. A. OVERTON[3], I. SAEZ[4], K. A. MOXON[5]; [1]UC Davis, Davis, CA; [2]Computer Sci., Univ. Of California Davis, Davis, CA; [3]Neurolog. Surgery, UC Davis, Ctr. for Neurosci., Woodland, CA; [4]Mount Sinai, New York, NY; [5]Biomed. Engin., Univ. of California Davis, Davis, CA

Abstract: Decision-making involves the coordinated activity of multiple brain areas and involves multiple sub-processes including reward evaluation, deliberation, and choice. Linear dynamical systems modeling has been shown to be capable of capturing the neural computations underlying sensorimotor activities. Here we examine its ability to provide insight into the neural computations relevant for choice. Neural activity from multiple brain areas in epilepsy patients undergoing intracranial electrophysiological monitoring (n=20) was recorded from several reward-related areas, including prefrontal and parietal cortices and deep temporal lobe structures, while patients played a neural economic decision-making task. Our task offered a choice between a safe bet or a risky gamble for a higher monetary reward. We applied different decoding algorithms to time-frequency decomposed neural data from all recorded regions in each patient. We developed four different models to predict the using of two different dimension reduction techniques: principal components analysis and linear dynamical systems and two different classifiers: Euclidean distance and dynamic time warping. Using a leave-one-out

paradigm, we achieved 71+/-3% trial-by-trial decoding performance with the LDS-DTW model, showing LDS can model the neural activity during choice. Results show that when there was no choice (win probability = 0/100%) the model failed to decode the subject's decision, suggesting the model was decoding risk. Secondly, the ability to decode decisions was independent of the win probability when there was a choice, suggesting the encoding of risky decisions is similar to that of less risky decisions. These results demonstrate that decoding cognitive states, in this case choices, from multi-areal intracranial data is possible. Future studies will need to examine the accuracy of more complex (e.g. non-linear) decoders, and to expand these decoding strategies into other brain states.

Disclosures: A. Roadarmel: None. **L. Peters:** None. **J.A. Overton:** None. **I. Saez:** None. **K.A. Moxon:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.21/W26

Topic: H.03. Decision Making

Title: Dynamic self-efficacy updating leads to optimistic overgeneralization

Authors: *J. LI[1], A. RADULESCU[2];
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Abstract: Humans often need to make predictions about future rewards by generalizing from similar past experiences. Positive overgeneralization occurs when a rewarding experience is attributed to multiple states of the environment. Self-efficacy is defined as one's belief in the capacity to execute actions that achieve desired outcomes. Appropriately updating self-efficacy based on past experience allows one to establish an accurate evaluation of current abilities and set realistic expectations of future rewards.
In this work, we propose dynamic self-efficacy updating as a cognitive mechanism for generalizing rewarding outcomes from one experience to another, and ask whether high self-efficacy update rates lead to overgeneralization of rewarding outcomes. Using a reinforcement learning (RL) approach, we introduce a learning rule that dynamically updates self-efficacy in appraisal of moving closer to a goal. We tested our model in a sequential grid-world environment and examined how different update rates for self-efficacy impact the underlying value representation. We found that for agents that update self-efficacy more quickly, the reward at the terminal states backpropagates to states closer to the start state, and the overall value of all states is higher. In other words, agents with more sensitive self-efficacy beliefs developed optimistic overgeneralized future reward expectations.
To test our model predictions in humans, we developed a novel behavioral paradigm to measure positive overgeneralization. A total of 24 online participants from Prolific completed a pilot

study, and data from 17 participants were included in the analyses after they met the inclusion criteria for learning the task. We found that participants who had high self-reported self-efficacy beliefs exhibited a significantly larger difference in RT between rewarding trials and non-rewarding trials, indicating positive overgeneralization ($t(16) = 2.23$, $p < .05$). This suggests that, consistent with our model, individuals with higher self-efficacy place greater valuation on rewarding trials compared to those with low self-efficacy.

Disclosures: J. Li: None. **A. Radulescu:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Topic: H.03. Decision Making

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Title: Parallel attention channels underlie exploration during learning of feature relevance in nonhuman primates

Authors: *P. TIESINGA[1], T. WOMELSDORF[2];
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Abstract: Inferring the behavioral relevance of visual features is difficult in multidimensional environments as many features could be important. To overcome this difficulty an attentional strategy can be used to serially test the importance of single features, but this approach accounts for only a fraction of choices during learning the relevance of features. To address this limitation, we propose a statistical approach that considers multiple feature channels in parallel and assigns discrete confidence states to features. The confidence states correspond to the degree features are attended, suggesting that attention is directed to multiple features in parallel during learning.
We tested this framework with a multidimensional attentional set shifting task in four nonhuman primates. Subjects were shown three objects that varied in multiple features and had to learn through trial-and-error which feature is the target. The target feature remained constant until criterion performance was reached and then switched to a new target feature that was either of the same or a different dimension (intra- vs extradimensional shifts), and that was shown on the same or on a new set of objects (same vs new object set). We formulate an input-driven hidden Markov model to predict the observed choices based on prior choices and reward outcome and determine the state transition matrices through maximizing the likelihood of the predicted feature choices and simultaneously infer the state of each feature channel for each trial.
We found that observed behavior is best described by considering for each feature four channel states that distinguishes whether a feature is (i) consistently chosen, (ii) explored and chosen above chance, (iii) chosen at random, or (iv) actively avoided. Subjects aggregate these attention-

channel states into choice-states that correspond to the number of hypotheses about target features simultaneously maintained. Choice states distinguish choice behavior ranging from 'exploiting a single feature', to 'exploring multiple features' to 'persisting with non-target features'. The model accounts for switch costs during set shifting: It transitions to the exploit state faster in the easier conditions (switching target features to new dimensions with new objects) and maintains an explore state longer for difficult (extradimensional shift with the same objects) conditions.
These results illustrate that learning in multidimensional environments is well accounted for by multiple parallel attention channels that determine which features are considered relevant, explored and attended during learning.

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Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.23/W28

Topic: H.03. Decision Making

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Title: Investigating brain-wide encoding through interpretable subspaces

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Abstract: In recent years, advances in recording technology have emphasized the importance of understanding population dynamics across multi-regional circuits. Various approaches have been used to understand coordinated dynamics across circuits. Broadly speaking, one can either define subspaces to quantify correlation by direct optimization for some property of coordinated dynamics or define subspaces by their single area content, and then measure correlations in these subspaces. A key challenge to the former method is heterogeneity of neural dynamics across time, sessions, or animals. If different subspaces are dominant at different time points, the leading subspaces found by direct optimization will reflect different mixes of these subspaces, complicating interpretation. Due to the lack of ground truth for between area interactions, interpretability and consistency across sessions and animals is particularly important in understanding coordinated population dynamics across brain areas. Here we analyzed a large-scale dataset with neural populations recorded in a single task across multiple brain areas. Using up to 5 Neuropixels probes, the dataset contains recordings from hundreds of neurons across the anterior lateral motor cortex (ALM) and its connected areas (medulla, midbrain, striatum, and thalamus). We first defined the coding subspace (CS), directions in activity that predict task-relevant variables and are thus highly interpretable. We found that the coding of these variables is highly correlated across areas. Then, through canonical correlation analysis we identified the between-area communication subspace (BACS), a subspace different from CS but with the highest between-area correlation. We further identified the motor subspace (MS) to characterize how much between-area correlation was affected by shared encoding of movement. We found that dynamics along the motor subspace had a larger contribution to between-area correlation along BACS than dynamics along the coding subspace. In other words, direct optimization approaches preferentially picked up on encoding of movement in each area. Between-area communication exhibited variability across subspace, epochs, and area pairs, making the interpretation of directly optimized subspaces more complex. Finally, we show that results of optogenetic perturbation could be predicted by correlation along CS but not along other subspaces. In summary, we studied between-area communication along subspaces of different representations and analyzed the relationships between these subspaces. Our work sheds light on understanding the structure of between-area coordination of dynamics.

Disclosures: Y. Liu: None. **S. Chen:** None. **Z. Wang:** None. **N. Li:** None. **K. Svoboda:** None. **S. Druckmann:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Title: Decision making via distributed evidence accumulation in neocortical networks

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Abstract: Despite the traditional view of parietal cortex as an important region for perceptual decisionmaking, recent evidence suggests that sensory accumulation occurs simultaneously across many cortical regions. We explored this hypothesis by integrating connectivity, cellular and receptor density datasets and building a large-scale macaque cortical model able to integrate conflicting sensory signals and perform a decision-making task. Our results reveal sensory evidence accumulation supported by a distributed network of temporal, parietal and frontal regions, with flexible sequential bottom-up or top-down modulation pathways depending on task difficulty. The model replicates experimental lesioning effects and reveals that the causal irrelevance of parietal areas like LIP for decision performance is explained by compensatory mechanisms within a distributed integration process. The model also reproduces observed temporal gating effects of distractor timing during and after the integration process. Overall, our work hints at perceptual integration during decision-making as a broad distributed phenomenon and provides multiple testable predictions.

Disclosures: L. Zou: None. **N. Palomero-Gallagher:** None. **S. Li:** None. **J.F. Mejias:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.25/W30

Topic: H.03. Decision Making

Support: ONR MURI Grant N00014-19-1-2373

Title: Core Beginnings of Consciousness: Eight Qualities of Subjective Experience, in Simulation

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Abstract: The nature of subjective experience, or consciousness, and its immanence across species is widely debated. We re-examine the problem through comparative analysis of nervous systems and behavior of both complex and simple animals and through agent-based computational simulations. We identify eight qualities associated with subjective experience critical to animals' fitness in term of foraging, defense, and reproduction: 1) Self-awareness, 2) Affect, 3) Goal- directedness, 4) Non-associative learning, 5) Pain, 6) Attentional mechanisms, 7) Dynamic use-dependent homeostatic plasticity, and 8) Reward-based learning and memory. Each of these qualities has been established in, or reasonably attributed to, simpler model animal systems like gastropod mollusks. These qualities emerge in a modular organization of information flow for decision shared across simple and complex animals. We have put them in computational simulations to represent simpler animals like the postulated ancestral Urbilaterian. The agent-based simulations Cyberslug [1] and ASIMOV [2] demonstrate these qualities. A ninth quality is added for more complex subjective experience in simple algorithms for episodic memory, allowing cognitive mapping and dynamic memory retrieval. This prepares for further enhancement with imagination, creativity, and social networking. In ASIMOV, the ninth quality is achieved with the addition of a Feature Association Matrix (FAM) [3] to show how the most basic associative learning rules can give rise to sequence learning, spatial learning, and simple episodic memory. ASIMOV was originally built on the core circuitry of the Cyberslug model of decision in foraging. We now expand the ASIMOV-FAM model for more dynamic and context-dependent behaviors, including hunting, homing, and resting behaviors. Our observations indicate that 1) most living systems may exploit their niches using subjective experience to optimize resource acquisition, defense, and reproduction, 2) consciousness may not be a particularly hard problem, and 3) computational entities may be constructed with builder-designed qualities of subjective experience for useful applications.

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[2]Gribkova, ED, Catanho, M & Gillette, R. Simple aesthetic sense and addiction emerge in neural relations of cost-benefit decision in foraging. *Sci. Rep.* **10**, 9627 (2020).
[3]Gribkova, ED, Chowdhary, G & Gillette, R. Cognitive Mapping and Episodic Memory Emerge From Simple Associative Learning Rules. *Neurocomputing*, In Press (2024).

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Poster

PSTR488: Computational Approaches to Neurocognition

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Topic: H.03. Decision Making

Support: NIH grant U01NS132788
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Title: A Neurocomputational Theory for Switching Motor Actions in Uncertain Environments

Authors: *S. ZHONG[1], D. CHATZIPARASCHIS[1], K. A. AGYEMAN[2], K. KARYDIS[1], N. POURATIAN[3], V. N. CHRISTOPOULOS[4];
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Abstract: Effective operation in uncertain environments requires the ability to select the best action, the flexibility to abandon obsolete actions, and switch actions in response to changes. Despite extensive research, the mechanism underlying action switching and how it relates to action selection and stopping remain elusive. A normative theory suggests that switching is an extension of stopping, during which a current action is inhibited by an independent pause mechanism before a new action is generated. The affordance competition hypothesis challenges this, proposing that switching could be implemented through a competition between the current and new actions. Building on this hypothesis and integrating dynamic neural field theory and stochastic optimal control theory, we developed a neurocomputational theory to model the processes of selecting, stopping, and switching actions. We tested the model predictions in healthy individuals (n=15, ages 21-42) performing reaching tasks in uncertain environments that often required stopping and switching. Our findings suggest that unlike stopping, switching does not necessitate a proactive pause mechanism to delay movement initiation. Once movement has begun, switching appears to involve an independent pause mechanism if the new target location is unknown. However, if the new target location is known beforehand, switching could be achieved by extending the action selection process, leading to longer “switch reaction times”. We assessed the applicability of the neurocomputational theory in developing bio-inspired robotic systems capable of adapting to dynamic environments. We deployed the model for dynamic target tracking using a robotic manipulator with visual feedback. The model demonstrated high end-effector positional accuracy, smooth trajectories, and reduced path lengths compared to a standard-of-practice baseline trajectory generator, offering a robust and dynamic-aware robotic manipulation approach. These findings provide insights into the computations underlying switching actions and contribute to the development of adaptive robotic systems capable of real-time decision-making in uncertain and dynamic environments. Our work opens new avenues for future neurophysiological investigations and the advancement of bio-inspired robotic platforms.

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Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

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Program #/Poster #: PSTR488.27/W32

Topic: H.03. Decision Making

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#NEXTGENERATIONEU (NGEU) - MNESYS - A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)

Title: Interpersonal coordination strategies in sensorimotor interaction

Authors: *C. DE VICARIIS, A. PROVAGGI, L. BANDINI, M. PARDINI, V. SANGUINETI; Univ. of Genoa, Genoa, Italy

Abstract: Interpersonal interaction or joint action is common in everyday life and involves perception and movement. The emergence of coordination through repeated interaction relies on the buildup of ‘trust’ between participants. Here we use a dyadic setup to test participants in sensorimotor versions of the classic Stag Hunt game. In this game, two hunters must independently choose whether to pursue a rabbit (getting a fair payoff, independent of what their partner does) or a stag (getting a better payoff, but only if they both decide so; otherwise they get zero payoff). The game has two Nash equilibria: the rabbit-rabbit strategy is risk-dominant with a low payoff and can be attained without collaboration; the stag-stag strategy is payoff dominant as both agents get a higher payoff, but only if they collaborate. The Stag Hunt game has been used to address the ‘trust’ emergence between two individuals.The experiment involved 18 dyads (36 participants). Participants were preliminarily instructed on the game rules and rewards schema but were not allowed to speak or look at each other. We tested two groups in which participants repeated the task for 90 trials. Participants in the Score group only gathered information about their partner at the end of each trial (display of partner position and payoff gained). In the Haptic group, participants experienced a resistive force during each motion depending on their own and partner’s selected action.To analyze the data, we used a probabilistic model of joint action, that includes a model of the partner’s next action which optimally combines prediction and observation, and an action selection module that accounts for multiple strategy choices. We identified the model parameters for each participant.Participants selected the stag with a greater probability and most dyads converged to the stag-stag solution, independently of the group. Model parameters analysis revealed that participants who performed in the Score group had smaller sensory noise, suggesting that the score provided a more reliable input. Further, the participants more prone to pick the stag strategy exhibited lower internal noise and greater retention rate, indicating that they represented their partner as more predictable.These experiments may contribute to characterizing participants’ ability to attribute mental states to others and to predict and describe behavior based on such mental states (theory of mind). Social skills deterioration or theory of mind deficits are a relatively early sign of dementia in otherwise normal functioning subjects, which points to using the proposed experimental paradigm in persons with early cognitive decline.

Disclosures: C. De Vicariis: None. **A. Provaggi:** None. **L. Bandini:** None. **M. Pardini:** None. **V. Sanguineti:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

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Program #/Poster #: PSTR488.28/W33

Topic: H.03. Decision Making

Support: NIMH Grant R01MH119383

Title: An algorithmic account for how humans efficiently learn, transfer, and compose hierarchically structured decision policies

Authors: *J.-J. LI, A. G. COLLINS;
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Abstract: Learning structures that effectively abstract decision policies is key to the flexibility of human intelligence. Previous work has shown that humans use hierarchically structured policies to efficiently navigate complex and dynamic environments. However, the computational processes that support the learning and construction of such policies remain insufficiently understood. To address this question, we tested 1,026 human participants on a decision-making task where they could learn, transfer, and recompose multiple sets of hierarchical policies. We propose a novel algorithmic account for the learning processes underlying observed human behavior. We show that humans rely on compressed policies over states in early learning, which gradually unfold into hierarchical representations via meta-learning and Bayesian inference. Our modeling evidence suggests that these hierarchical policies are structured in a temporally backward, rather than forward, fashion. Taken together, these algorithmic architectures characterize how the interplay between reinforcement learning, policy compression, meta-learning, and working memory support structured decision-making and compositionality in a resource-rational way.

Disclosures: J. Li: None. **A.G. Collins:** None.

Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.29/W34

Topic: G.03. Motivation

Title: Gender differences across response inhibition and reward feedback tasks

Authors: *M. BERRY[1], N. MATTANAH[1], Y. CHEN[1], M. VALENÇA[1], S. NAHABEDIAN[1], D. BUTLER[1], J. S. MOSER[2], E. BERNAT[3];
[1]Univ. of Maryland, Col. Park, College Park, MD; [2]Michigan State Univ., East Lansing, MI; [3]Psychology, Univ. of Maryland, College Park, MD

Abstract: Objective: The present study assessed gender differences in theta (3-7 Hz) activity for three common medial-frontal theta (MFT) generating components: Error-Related Negativity (ERN), N2, and Feedback-Related Negativity (FRN). Studies related to ERN have largely suggested increased amplitude for males compared to females which may indicate greater use of cognitive resources during performance monitoring tasks (Fischer et al., 2016; Larson et al., 2011). There is some evidence that occipital theta activity may differ between sexes as it pertains to stimulus processing (Kamarajan et al., 2008). Findings from Doors (Crowley et al., 2013), Go-Nogo (GNG) (Gaillard & Rossell, 2022), and Flanker tasks (Ramos-Loyo et al., 2022) have been inconsistent concerning sex differences. In this current project, we examined sex differences across these three tasks. We hypothesized increased MFT activity for males relative to females for the Flanker task. We hope these findings will advance our understanding of sex differences as they pertain to crucial cognitive functions. Methods: Our sample consists of adults derived from the Michigan Longitudinal Study (MLS) with data collected using a 64-channel Biosemi EEG system. Task outcomes included results from a GNG task (N = 173, females = 103; age: M = 34.21, SD = 5.95), Doors task (N = 153, males = 62, age: M = 34.25, SD= 6.14), and a Flanker task (N=156, females = 95, age: M=34.21, SD = 5.80). Results: Paired samples t-tests were conducted to compare results across genders in the medial-frontal and occipital regions. We did not find robust sex differences in the Flanker task. Significant sex differences in activity were found across both regions in Doors Gain and Loss, as well as in GNG Nogo, with females showing greater power compared to males. There was a significant effect of gender on MFT, $t(146.49) = 2.86$, $p < 0.01$, and on occipital theta (OT), $t(147.74) = 3.77$, $p < 0.01$ in Doors Loss. These differences were detected in Doors Gain as well in MFT, $t(150.7) = 2.37$, $p < 0.05$, and in OT, $t(145.26) = 2.88$, $p < 0.01$. Females also showed increased power compared to males in the GNG Nogo condition across MFT, $t(168.13) = 2.18$, $p < 0.05$, and OT $t(169.09) = 3.7$, $p < 0.01$. However, in the Go condition, significant sex differences were only observed in the occipital region, $t(170.11) = 2.62$, $p < 0.01$. Discussion: Our findings suggest increased salience and visual cortex activity (MFT and OT, relatively) for females during Doors and GNG, but not in the Flanker task. Future directions include analysis using interchannel phase synchrony methods to assess potential sex differences in functional connectivity.

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Poster

PSTR488: Computational Approaches to Neurocognition

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR488.30/W35

Topic: H.13. Schizophrenia

Support: NIH P50MH119569

Title: Computational indices of state-based learning predict symptom severity in early psychosis

Authors: *C. S. CHEN[1], C. DEMRO[2], S. SPONHEIM[2], N. M. GRISSOM[3], B. R. EBITZ[4], A. D. REDISH[5], S. VINOGRADOV[2], A. W. MACDONALD III[6];
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Abstract: To adapt and succeed in changing environments, the brain must develop accurate representations of the current state of the environment and use feedback to learn the structure of these states. Deficits in state representation and reinforcement learning have been implicated in individuals with psychosis spectrum disorders. The goal of this study was to examine the link between state-based learning strategy and interindividual variability in cognitive functions, with implications for predicting symptom severity from computational indices of state representation in people with psychosis. We recruited 75 Early Psychosis (EP) participants and 68 Healthy Controls (HC) and administered a dynamic value-based decision making task (the restless bandit task with three choices). Options were indicated with Gabor filter stimuli of differentiable frequencies, appearing at three locations (randomly assigned) on each trial. Reward probability for each option changed slowly over time. This translational task produces latent cognitive strategies of exploration and exploitation. We leveraged computational modeling approaches to extract parameters that capture latent cognitive strategies. We fit a Hidden Markov Model to infer latent exploration and exploitation states from choices and found that EP subjects explored more than controls, due to a higher probability of transitioning to an exploratory strategy. Early Psychosis subjects showed higher win-shift out of exploitation state than controls, which was associated with greater negative psychotic symptom severity among the Early Psychosis group. To understand the factors that contribute to over-exploration in patients, we fit a Bayesian learning model to identify latent cognitive parameters driving the variability in exploratory strategies. The Bayesian model assumes adaptive learning rate based on uncertainty estimates, formalizing value updating with a Kalman filter. We found that patients with psychosis weighed uncertainty more in their decision making, potentially contributing to their increased exploration. These results suggest that people with Early Psychosis over-explore, potentially due to overweighting of environmental uncertainty, which in turn drives them to switch to an exploratory strategy too soon.

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Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

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Program #/Poster #: PSTR489.01/W36

Topic: I.03. Anatomical Methods

Support: GRF Grant Ro2327/13-2

Title: Cortical brain organoid slices (cBOS) are a robust model system for the functional study of human-derived neural cells in intact minimal networks.

Authors: *W. KAFITZ[1], L. PETERSILIE[2], C. ROSE[3];
[1]Inst. of Neurobio., Heinrich Heine Univ. Düsseldorf, Düesseldorf, Germany; [2]Inst. of Neurobio., Heinrich Heine Unniversity Düsseldorf, Düsseldorf, Germany; [3]Inst. of Neurobio., Heinrich Heine Univ., Düsseldorf, Germany

Abstract: Studying the human brain and its development is crucial if we want to understand how neurological and neurodevelopmental disorders arise. However, the complexity of the human brain hampers the establishment of approaches aiming at unveiling mechanistic disease aspects. A major breakthrough came from the discovery that human pluripotent stem cells (hPSCs) can be coaxed into three-dimensional (3D) structures that recapitulate features of the developing human brain. These brain organoids represent a powerful tool as they reproduce several key steps of neural maturation. However, with continued growth in culture, they also may inherit hypoxic/ischemic conditions and insufficient nutrient supply to their inner core, resulting in cell death and restricted cellular differentiation. In addition, the structure of large-diameter 3D brain organoids complicates the direct probing of neuronal functionality. To circumvent these limitations, several laboratories have recently introduced long-term culturing of slices prepared from whole-brain cerebral organoids grown at the air-liquid interphase (ALI-COs). Here, we followed this strategy and report a protocol for establishing robust cortical brain organoid slices (cBOS) derived from regionalized cortical organoids that can be maintained in prolonged culture at the air-liquid interface. Given the homogenous and spherical morphology of cortical organoids, cBOS show a uniform roundish appearance and develop well-organized and connected structures of neurons and astrocytes. Single-cell electrophysiological recordings revealed subthreshold synaptic inputs and neuronal action potential firing whereas calcium imaging demonstrated spontaneous intracellular calcium transients as well as large synchronous oscillations upon disinhibition, indicating that cBOS represent a functionally active, synaptically-connected neural network. Exposure of cBOS to pharmacological inhibitors of glycolysis and oxidative phosphorylation to mimic hypoxic-ischemic conditions resulted in a rapid increase in intracellular calcium concentrations. The increase in cellular calcium was accompanied by an immediate loss of cellular ATP. In conclusion, these results demonstrate that ATP depletion under ischemic conditions induces cellular calcium loading in a developing human cortical network in culture. Furthermore, they suggest that cBOS may serve to elucidate the molecular pathways and consequences of ischemia-induced rapid ion dysregulation, thereby helping to identify novel cellular targets to counteract cell damage in the developing human brain during metabolic failure.

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Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.02/W37

Topic: I.03. Anatomical Methods

Support: NSERC Grant DGECR- 2021-00228 to JM

Title: Ex vivo human brain volumetry: validation of magnetic resonance imaging measurements

Authors: *A. GÉRIN-LAJOIE[1], E.-M. FRIGON[1], W. ADAME-GONZALEZ[2], M. DADAR[3], D. BOIRE[1], J. MARANZANO[1,2];
[1]Anatomie, Univ. du Québec à Trois-Rivières, Trois-Rivières, QC, Canada; [3]Biomed. Engin., [2]McGill Univ., Montreal, QC, Canada

Abstract: Background - The volume of *in vivo* human brains is determined with various magnetic resonance imaging (MRI) protocols to assess the atrophy associated with neurodegenerative diseases. However, these volume measurements determined *in vivo* have not been validated against a gold standard assessment. Here, we propose a validation of the *in vivo* MRI volume by scanning human brain specimens *ex vivo-in situ*, which allows the extraction of the brain after the scan to validate its volume against the gold standard method of water displacement (WD). **Methods** - We acquired T2-weighted images (3T MRI; 3D-space) of five anatomical heads (N=5) fixed with an alcohol and formaldehyde solution routinely used in anatomy laboratories, and segmented the gray and white matter of the hemispheres, brainstem and cerebellum using two methods: 1) a semi-manual intensity-based threshold segmentation using the Display software (MINC-ToolKit, McConnell BIC), which takes up to 21 hours per case, and 2) an automatic Deep-Learning-based segmentation using the SynthSeg software (Billot et al 2023), which takes about 3 minutes per case, to obtain the total volume of each brain in cubic centimeters (cm^3). The brains were subsequently extracted and their volumes determined by the WD method, before and after the removal of meninges and after a midsagittal cut (to allow water penetration into the ventricles). Volumes were compared using a repeated measures ANOVA. Intra-rater variability of the WD method was evaluated with an intraclass correlation coefficient (ICC). Intra- and inter-rater variability of the semi-manual and automatic MRI segmentation methods were evaluated with a Dice kappa similarity coefficient. **Results** - Mean brain volumes, in cm^3, were 1347.40±65.20 with meninges, 1160.80±54.70 without meninges, 1148.20±56.91 with both hemispheres, 1033.30±35.09 by semi-manual segmentation (SMS) and 1080.11±44.19 by automatic segmentation (AS). The brain volume with meninges was significantly different from all other volumes (in order, $p=0.001$; $p<0.001$; $p=0.006$; $p=0.002$). A significant difference was observed between brain volumes without meninges and by AS ($p=0.044$). All other volume comparisons were not significantly different. Intra-rater variability ICC of the WD method was 0.904 with meninges, 0.984 without meninges and 0.998 with both hemispheres. Intra- and inter-rater variability of the SMS method and differences between the SMS and AS masks had Dice kappas of 0.9745, 0.9809 and 0.9481, respectively. **Conclusion** - Both the MRI SMS and AS methods are valid for determining human brain volumes, but the MRI AS method gives equally valid volumes in a much shorter time.

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Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR489.03/W38

Topic: I.03. Anatomical Methods

Title: Presenting a project using cranes in the human anatomy and neuroanatomy laboratory.

Authors: *V. S. FAZAN[1], **A. G. RODRIGUES**[2];
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Abstract: The human anatomy laboratory is an essential environment for medical education and research, facilitating hands-on learning and exploration of the intricate structures of the human body. One aspect that has gained attention in recent years is the utilization of cranes to lift and move cadavers within these laboratories, offering several distinct advantages. We present and discuss the benefits of using cranes for moving cadavers in anatomy laboratories. Traditional methods of cadaver transportation often involve manual lifting and carrying, which can be physically demanding for instructors, students, and researchers. Cranes provide a practical solution by enabling controlled and precise movement, reducing the risk of strain-related injuries. Additionally, cranes offer the flexibility to transport cadavers to various stations without disrupting the learning process. Moreover, the use of cranes enhances safety by minimizing the potential for contamination and damage to cadavers. By eliminating the need for frequent handling, the risk of cross-contamination is mitigated, and maintaining a hygienic environment crucial for accurate anatomical study. Cranes also help preserve the integrity of cadavers, ensuring that valuable specimens are not compromised through improper handling. In terms of educational efficacy, cranes optimize the teaching experience in anatomy laboratories. Instructors can effortlessly maneuver cadavers to showcase specific anatomical features from different angles, enhancing students' understanding and facilitating interactive discussions. This approach enhances the learning process, enabling a comprehensive exploration of complex anatomical structures. In conclusion, the integration of cranes in human anatomy laboratories revolutionizes the movement of cadavers, offering advantages such as improved safety, reduced physical strain, and enhanced educational outcomes. This innovation represents a significant step forward in anatomical education and research, fostering a more efficient and effective learning environment for aspiring medical professionals.

Disclosures: V.S. Fazan: None. **A.G. Rodrigues:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR489.04/X1

Topic: I.03. Anatomical Methods

Support: NSERC Grant DGECR- 2021-00228 to JM
NSERC Grant BESC D 3-559015-2021 to EMF
NSERC Grant RGPIN-2018-06506 to DB

Title: 7T MRI to histology alignment of *ex vivo* human brain blocks fixed with solutions used in gross anatomy laboratories

Authors: *E.-M. FRIGON[1], A. GÉRIN-LAJOIE[1], J. FOUQUET[2], Y. ZEIGHAMI[3,2], D. BOIRE[1], M. DADAR[3,2], J. MARANZANO[1,3];
[1]Univ. Du Quebec A Trois-Rivieres, Trois-Rivieres, QC, Canada; [2]Douglas Res. Ctr., Montreal, QC, Canada; [3]McGill Univ., Montreal, QC, Canada

Abstract: Post-mortem brain tissue is commonly obtained from brain banks that provide small tissue samples, while gross anatomy laboratories could become a source of full brains to neuroscientists. However, these are preserved with solutions appropriate for dissections, whose chemical compositions differ from the classic neutral-buffered formalin (NBF) used in brain banks. Our previous work has shown that two of these solutions, a saturated salt solution (SSS) and an alcohol-formaldehyde solution (AFS) preserve antigenicity of the main brain cell populations. Since histology is the gold standard in neuroscientific research and magnetic resonance imaging (MRI) is the most common imaging modality used, the effect of anatomy laboratory solutions on MRI-histology registration needs to be assessed. Hence, our goal was to compare the degree of difficulty aligning MRI and histology slices of human brain blocks fixed with NBF, SSS and AFS.We used 6 human brains fixed in our anatomy laboratory (SSS=2; AFS=2; NBF=2), cut into 3cm^3 blocks and scanned in a 7T Bruker animal MRI scanner (0.13*0.13*0.5mm^3). The MRI scans were qualitatively assessed for gray to white matter (GM-WM) contrast. Blocks were cut into 40µm sections (parallel to the high resolution MRI plane) and stained with Cresyl violet (CV), Prussian blue (PB), Luxol fast blue (LFB), Hematoxylin-Eosin (H&E), and Bielchowsky's technique (Biel.). The ten labeled sections per specimen (two per stain) were scanned using a slide scanner microscope. The first step of our registration pipeline consisted in tagging anatomical landmarks in the T2-TurboRare MRI and in histology slices using Register (MincToolKit, McConnell BIC), to create an initial alignment followed by automatic linear and non-linear registration. The higher the number of tags, the more difficult the process is, potentially impacting the quality of the alignment. Requiring a minimum of 4 tags to give an output, we created three qualitative categories according to the number of tags to compare the 3 fixatives: Easy=4-6; Intermediate=7-9; Difficult= >10. MRI showed very good GM-WM contrast in AFS and NBF-specimens, and lower contrast in SSS ones. We found only 3 (PB of Case 2; Biel. of Case 4; CV of Case 5) and 7 sections (CV, PB of Case 1; LFB of Case 2; H&E of Case 3; H&E, Biel., PB of Case 4; CV of Case 5) that were graded as difficult or intermediate respectively. Nevertheless, we achieved an equal high quality of registration alignments based on the visual assessment regardless of the number of tags and fixative used.

These results demonstrate the feasibility of using brains from anatomy laboratories in *ex vivo* MRI and histology investigations.

Disclosures: E. Frigon: None. **A. Gérin-Lajoie:** None. **J. Fouquet:** None. **Y. Zeighami:** None. **D. Boire:** None. **M. Dadar:** None. **J. Maranzano:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR489.05/X2

Topic: I.03. Anatomical Methods

Support: R01-AG075727
R01-AG062831

Title: From Freezing to Fluorescence: A Simple and Effective Thawing Method for Histological Studies

Authors: *R. E. ROBINSON[1], A. GRAY[2], F. MORTAZAVI[3];
[1]Anat. & Neurobio., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA; [2]Biomed. Engin., Boston Univ., Boston, MA; [3]Anat. and Neurobio., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Fresh-frozen tissue serves well for molecular methods but falls short for histology. Fresh-frozen tissue benefits from fixation and cryoprotection before slicing and staining to mitigate freezing artifacts and to avoid severe damage to the tissue while processing for histology. Unfortunately, those same protective measures render tissue unsuitable for molecular and biochemical assays, necessitating separate tissue inventories for each application. This limits overall utility for researchers. Here, we present a simple, reliable, inexpensive, novel method for thawing previously fresh-frozen tissue so that it is preserved for histological processing. First, glycerol was diluted to 30%, 20%, and 10% concentrations containing 2% DMSO. The 30% and 20% glycerol solutions were chilled to slush (-9°C and -5°C, respectively) and the 10% glycerol solution held at 4°C. Tissue was first submerged in the (-9°C) 30% glycerol solution for 5 minutes, then transferred to the (-5°C) 20% glycerol solution for 6 hours. Finally, tissue was transferred to the 4°C 10% glycerol solution and rested at 4°C for a further 24 hours. Following the stepdown glycerol thawing, tissue was fixed by immersion in a 4°C 4% paraformaldehyde solution for 2 days. Finally, the tissue was cut on a vibratome into 40µm-thick sections and subjected to fluorescent IHC labeling protocol to label neurons, glia, and vascular structures. The IHC labeling protocol used on this thawed tissue was identical to that used on perfusion-fixed, cryoprotected tissue. Tissue was also subjected to birefringence microscopy (BRM) imaging, which demonstrates myelin integrity with no histological processing and thus clearly reveals artifactual defects created during any additional processing. Tissue sections subjected to our glycerol stepdown thawing method were compared to sections that were prepared conventionally

for histological processing (ie. perfusion-fixed, post-fixed, and cryoprotected). The untreated tissue exhibited significant cellular integrity breakdown making IHC labeling unreliable and difficult to interpret. Tissue treated with the stepdown thawing method was visually indistinguishable from tissue processed with typical in-house tissue processing methods optimized for IHC. Successful implementation of this post-thawing process allows the researcher to directly flash-freeze all tissue upon harvesting knowing it will retain its utility across a broad spectrum of analytical methods.Top of Form

Disclosures: R.E. Robinson: None. **A. Gray:** None. **F. Mortazavi:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.06/X3

Topic: I.03. Anatomical Methods

Support: P50-MH100031
P51-OD011106
R01-MH046729
R01-MH081884
R01-MH107444
R21-DA040717

Title: Multivariate clustering and validation for parcellating the prefrontal cortex in a large sample of rhesus macaques

Authors: *C. DRZEWIECKI[1], J. A. OLER[2], R. M. BIRN[3], A. J. SHACKMAN[4], A. ALEXANDER[5], N. H. KALIN[6], A. S. FOX[7];
[1]UC Davis, Davis, CA; [2]Psychiatry, Univ. of Wisconsin, Madison, WI; [3]Psychiatry, Univ. of Wisconsin - Madison, Madison, WI; [4]Univ. of Maryland, College Park, MD; [5]Univerisity of Wisconsin Madison, Madison, WI; [6]Psychiatry, Univ. of Wisconsin-Madison Sch. of Med., Madison, WI; [7]Psychology, Univ. of California - Davis, Davis, CA

Abstract: The prefrontal cortex (PFC) is a functionally heterogeneous brain region made up of architectonically distinct subregions based on various factors, including cytoarchitecture, anatomical connectivity, functional connectivity, and task-related activation patterns. These subdivisions make up larger cortico-cortical networks, which have been identified in the PFC of humans and nonhuman primates and are implicated in emotional behaviors. Using resting state fMRI data from a large sample of young rhesus macaques (n=378) we employed a data-driven method to parcellate the PFC based on intrinsic functional connectivity. Our approach entailed multivariate clustering at the individual level, grouping brain regions by their intrinsic functional connectivity patterns. Specifically, we computed pairwise correlations between fMRI time series across 45,914 voxels per subject, followed by dimensionality reduction using UMAP and

clustering via HDBSCAN. This process yielded cluster-specific assignments for each voxel. We then quantified inter-subject similarity to ascertain the consistency of clusters at the group level. Resulting parcellations were validated using qualitative and quantitative measures of reproducibility both within and across subjects. Initial results from our analysis identify clusters of PFC connectivity that roughly align with current boundaries determined by cortical atlases. Bilateral parcellations correspond to known subregions of OFC, dlPFC, and ACC. Quantitative comparisons of functional coupling with data-derived subregions exhibited similarities to coupling patterns observed with manually annotated subregions. Split-half analysis demonstrated up to ~89% correspondence at the group level, suggesting the capacity to consistently identify and reproduce specific patterns within individual subjects. These preliminary results suggest the efficacy of our approach in reliably identifying cortical subregions. Subsequent investigations will leverage these parcellations to understand the relationship between functional networks and established anatomical connections across prefrontal regions.

Disclosures: C. Drzewiecki: None. **J.A. Oler:** None. **R.M. Birn:** None. **A.J. Shackman:** None. **A. Alexander:** None. **N.H. Kalin:** None. **A.S. Fox:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.07/X4

Topic: I.03. Anatomical Methods

Support: NIH Grant R01MH121735

Title: Infant inhibited temperament is associated with sex-specific alterations in prefrontal white-matter in adult primates

Authors: *L. J. CAMPOS[1], D. P. TROMP[2], C. M. DRZEWIECKI[3], J. P. CAPITANIO[4], A. S. FOX[5];
[1]Psychology, Univ. of California, Davis, Davis, CA; [2]Psychiatry, Univ. of Wisconsin, Madison, WI; [3]UC Davis, Davis, CA; [4]California Natl. Primate Res. Ctr., Univ. of California Davis, Davis, CA; [5]Psychology, Univ. of California - Davis, Davis, CA

Abstract: Anxiety disorders are among the most common and debilitating mental illnesses in the world, with women more likely to be affected. Although most individuals don't develop anxiety and depressive disorders until adolescence and young adulthood, decades of research has identified early-life inhibited temperament (IT) as a risk factor for the later development of these disorders. Identifying the neurobiological mechanisms that contribute to this risk may open the door to new treatments. Recent studies have suggested that differences in white matter microstructure in the Uncinate Fasciculus may be important in the development of anxiety disorders in males, but not females. Here, we used diffusion tensor imaging (DTI) to examine sex-specific differences in the white-matter pathways that underlie inhibited temperament in

rhesus monkeys. 76 adult rhesus monkeys (macaca mulatta; 29 female; Mean Age=5.01 years) previously assessed for inhibited temperament at ~3-4 months were selected for this study. We collected two 60-direction diffusion weighted imaging (DWI) scans per animal. Data were processed using established methods, including tensor normalization. Whole-brain voxelwise analyses between inhibited temperament and fractional anisotropy (FA; a measure of white-matter integrity) were conducted using FSL's randomise. Results demonstrated significant correlations between infant inhibited temperament and adult FA in a number of regions, including a positive correlation with FA in the subgenual prefrontal cortical white-matter ($p<0.01$, two-tailed uncorrected). Further analysis revealed that females showed this positive correlation between IT and FA in the subgenual prefrontal cortical white matter ($p<.05$, two-tailed, uncorrected). Additionally, a sex by IT interaction also revealed a significant cluster in subgenual prefrontal white matter ($p<.05$, two-tailed, uncorrected).These data provide initial evidence that subgenual white-matter integrity in pathways linking prefrontal regions to key structures of the extended amygdala could be involved in the risk to develop stress-related psychopathology in a sex-specific way. These findings may provide insight into the well-established sex differences in the risk to develop anxiety and depressive disorders.

Disclosures: L.J. Campos: None. **D.P. Tromp:** None. **C.M. Drzewiecki:** None. **J.P. Capitanio:** None. **A.S. Fox:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.08/Web Only

Topic: I.03. Anatomical Methods

Title: Engineering well-characterized and environmentally-relevant nano and micro plastics for experimental mouse models

Authors: *L. L. SHIELL[1], E. VIVERETTE[2], A. B. WEST[2];
[1]West Lab., Duke Ctr. for Neurodegeneration Res., Durham, NC; [2]Dept. of Pharmacol. and Cancer Biol., Duke Univ., Durham, NC

Abstract: Engineering well-characterized and environmentally-relevant nano and micro plastics for experimental mouse models
Lauren L. Shiell, Elizabeth G. Viverette, Andrew B. West
Duke Center for Neurodegeneration and Neurotherapeutics, Department of Pharmacology and Cancer Biology, Duke University
The ingestion of plastics presents a significant concern for human health as the mass of plastic estimated to be ingested by individuals is increasing every year. Some studies suggest that there is the relative consumption of plastic found in 50 shopping bags per person per year. However, the implications for human health are complex due to the diverse nature of polymer structure and surface charges which could significantly vary biodistribution and interactions with other

molecules like proteins, lipids, and nucleic acids. Current studies often rely on pristine engineered nanobeads, usually polystyrene which is relatively rare in the environment, to understand nanoplastic biology. However, these nanobeads do not mimic environmentally relevant particles in both polymer compositions, surface chemistries and morphologies.
To generate particles for research purposes that better mimic what we are exposed to in daily activities, we have developed a methodology for the production of particles with differing surface charges and shapes from the most common types of plastic pollutants. Sourced recycled starting plastics were obtained from different manufacturers and cryomilled to micro and nano mixtures, and exposed to a novel environmental chamber to simulate exposures in the marine environment in years- to decades ranges. Particles are characterized through orthogonal informative suites of approaches that will include empirically measured ZetaPotential for surface charges, and shapes defined by light-scattering and Cryo-EM. Bioavailability of these particles will be studied in young and aged mice, and in mouse models of disease. The goal is to understand the chemical requirements of plastic pollutants to access different compartments in mammals and what their contribution might be to disease risk and progression.

Disclosures: L.L. Shiell: None. **E. Viverette:** None. **A.B. West:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.09/X5

Topic: I.03. Anatomical Methods

Support: RF1MH128969
UM1NS132358

Title: An automated monoclonal antibody validation pipeline to support reliable volumetric profiling of molecular targets

Authors: K. K. THIRTAMARA[1], ***J. SAYED**[2], A. IZUMI[2], X. WANG[3], S. MU[2], W. WANG[4], Z. WU[5];
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Abstract: Lack of reliable antibodies is a serious financial drain on research dollars in addition to wasted time and effort in generating non-reproducible data. Only a subset of commercially available antibodies has been validated to recognize their intended targets. A large number of them are polyclonal antibodies that are not renewable to support desired reproducibility in large-scale and long-term applications. Monoclonal antibodies (mAb) can offer more consistency and scalability, and are also better suited for quantitative analysis. Despite decades of community effort in producing and distributing mAb resources, their use is still limited by availability and

lack of systemic validation in defined applications across different species. We are leading concerted effort to screen and validate mAb from commercial vendors and antibody libraries generated through partners (Addgene, NeuroMab, JHU/CDI) funded by BICAN, for robust immunolabeling application. We aim to generate a comprehensive and openly accessible mAb resource for the neuroscience community, extend the validation of mAbs beyond mouse brain tissue and include both non-human primate and the human brain. 3D whole mount labeling on cleared brains (and other organs) is a unique tool to study spatial distribution of different cell types as well as a platform to reliably perform quantitative marker analysis through the use of validated mAbs. To integrate this into our existing workflow, we established a validation pipeline for immunolabeling that is also compatible with advanced tissue clearing and labeling. We screened over 150 recombinant antibodies generated by Addgene using the Neuromab. This was followed by another 400 from the Neuromab library on our automated immunostaining platform. Image acquisition was also automated for high throughput generation of high-quality images. In parallel, we automated image format conversion and cloud storage for web-based sharing and visualization. Utilizing Python scripts, we transformed slice scanner imaging formats into OME-Zarr format, a format that grew out of the next-generation file format (NGFF) effort of the Open Microscopy Environment consortium. This ensures gigabyte-sized full-resolution images can be accessed and inspected by fellow researchers through Neuroglancer format. The links are made available on our own website (https://mab3d-atlas.com/) and shared with our partners (https://www.addgene.org/antibodies/all/) complete with protocol information. We aim to turn this into a comprehensive and open-source platform for the larger neuroscience community.

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Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.10/X6

Topic: I.03. Anatomical Methods

Support: NIMH for SBIR Grant R44MH119989

Title: Lowering the Barrier to Tissue Clearing: Undergrad Approved

Authors: *N. HYMAN, N. GUANZON, E. BLAES, C. REDD, D. G. WHEELER; Translucence Biosystems, Irvine, CA

Abstract: Despite great advances in tissue labeling and imaging technology, until very recently high-resolution imaging of more than a few hundred microns into a tissue has required sample slicing and mounting on slides. Providing access to the intricate anatomy of the whole intact brain, tissue clearing offers neuroscientists unbiased and complete views of brain anatomy and

function. While scientifically and statistically relevant, wide adoption of these techniques has proven slow. In this poster, I will uncover how I, as an undergraduate researcher, was able to master these techniques with little lab experience. With minimal hands-on help from Translucence Biosystems, I was able to generate 3D whole-brain anatomics data. I utilized iDISCO-based tissue clearing kits, imaged on a ZEISS Lightsheet Z.1 microscope using the Translucence Biosystems Mesoscale Imaging System, and quantified my samples using the Translucence Biosystems machine learning teravoxel toolkit (3TK) to produce regionalized read-outs of cellular patterns across 100's of brain regions. I processed five samples: three whole mouse brains and two hemispheres. One whole brain and two hemispheres were stained for Npas4 and cFos, two immediate early gene (IEG) products. Expression of cFos is driven by Ca2+ -signaling downstream of neuronal activity and is commonly used to mark active neurons. However, cFos expression is also driven by cAMP elevations and signaling pathways engaged by neurotrophins or other paracrine factors. In contrast, Npas4 expression is neuron-specific and tightly tuned to Ca 2+ -dependent signaling pathways. The concurrent measurement of these two IEGs allowed for the whole-brain machine learning quantification of recent neuroactivity in the samples. The two additional whole brains were stained for Tyrosine Hydroxylase (TH) and Iba1. TH is a marker for dopaminergic neurons in the CNS, enabling ultra-high-quality visualizations of the mesolimbic system and its relevant regions. Paired with 3D volume quantification, I was able to quantify average fluorescence intensity in different regions across the brain. Using antibodies targeting the microglial protein Iba1, I was able to visualize microglia across the entire brain. This visualization paired with AI-powered segmentation workflows allowed for the whole-brain quantification of microglia distribution and intensity. While adoption of tissue clearing has been slow, this work suggests that its implementation is more feasible than many researchers realize.

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

Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR489.11/X7

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

Support: Z01ES090089

Title: Mesoscopic analysis of cholinergic neurons in the mouse brain

Authors: *R. O. GORAL[1], J. L. YAKEL[2];
[1]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]Neurobio., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

Abstract: Acetylcholine (ACh) neurons in the central nervous system (CNS) coordinate the neural network activity in the brain to enable learning and memory. Disturbed ACh signaling has been linked to many brain disorders. Moreover, some ACh neurons co-transmit GABA which has been linked to essential brain functions. However, it is still unknown where, when, and how GABA co-transmission from ACh neurons contributes to brain function.We set out to assess the distribution of GABAergic ACh neurons in the mouse brain. To do so, we used a variety of transgenic mouse models that label ACh neurons with fluorescent markers. We employed a workflow of tissue clearing and light-sheet fluorescence microscopy to image ACh neurons in entire brain hemispheres. Using intersectional genetics, we quantified ACh neurons as well as ACh neuron subpopulations. We discovered that many ACh neurons express or previously had a GABAergic fate.

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Poster

PSTR489: Sample Preparation and Novel Probes

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Program #/Poster #: PSTR489.12/X8

Topic: I.03. Anatomical Methods

Support: NIH Grant R61 HL159948
NSF Expedition Award IIS-2123781

Title: Development of a thermo-sensitive hydrogel based automatic manipulator for rapid transport of thin tissues

Authors: *S. KANG[1], H. KONG[2];
[1]Univ. of Illinois, Urbana-Champaign, Urbana, IL; [2]Chem. & Biomolecular Engin., Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL

Abstract: Handling thin layers of cells are essential for several applications, from putting stem cell sheets for regenerative medicine to transporting brain slices for analysis. However, handling the cell sheets without defects is challenging due to their thin, frail, and wet nature. Although several approaches have been suggested, they often require complicated procedures, long working times, and additional processes for removing supporting materials. In this study, we

developed a cell sheet manipulator that assembles complex 'living' tissue and hybridizes it with electronics, creating a user-friendly device. The manipulator consists of a thermally switchable adhesive system and an electrical power unit. The temperature-controlled volume change of the micro-channeled hydrogel manipulates negative pressure and subsequent suction force. Therefore, the manipulator lifts and releases target substrates in response to heat control. Furthermore, the manipulator was combined with a 3-axis motorized stage for automatic cell sheet transfer. The soft manipulator can rapidly grip or release various substrates such as silicon wafers, glass wafers, and cell sheets within 10s, and the gripping and releasing function of the manipulator was conducted under 40℃. Plus, the switchable adhesive system showed a high on/off switching ratio of adhesion strength in wet conditions. The soft manipulator can be repetitively used over 50 times in wet conditions and the manipulator can transfer substrates with both dry and wet surfaces. Furthermore, the manipulator installed in motorized stage for automatic cell sheet transfer between multiple locations from user command. The manipulator can be used for the implantation of cell layers as regenerative medicine. Plus, this system would give an insight into an automatic neural activity monitoring system utilizing brain slices and multiple microelectrodes arrays. This work was partially supported by grants from the National Institutes of Health (R61 HL159948) and the National Science Foundation Expedition ‘Mind in Vitro’ Award (IIS-2123781).

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Poster

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Program #/Poster #: PSTR489.13/X9

Topic: I.03. Anatomical Methods

Support: NIH R01DK129315
NIH DP2AT010875

Title: Three-dimensional single cell morphology of transcriptionally distinct classes of neurons

Authors: S. H. MOHAMED[1], M. K. H. FOYSAL[1], A. L. HARB[1], A. BEYDER[2], U. K. MARKLUND[3], *D. R. LINDEN[1];
[1]Physiol. and Biomed. Engin., [2]Med., Mayo Clin., Rochester, MN; [3]Med. Biochem. and Biophysics, Karolinska Institutet, Stockholm, Sweden

Abstract: Relating structure to function has dominated neuroscience since the creation of the Neuron Doctrine. Recent advances in single cell and spatial transcriptomics have greatly advanced our understanding of the diversity of neurons and led to entirely new neuron classification schemes. However, there has been relatively little work to advance of understanding of neuronal structure in relationship to these new classification schemes. To address this gap in knowledge, we have developed a robust experimental pipeline to identify the

three-dimensional structure of single neurons targeted through class-specific promoter-driven recombinases and double-inverse orientation AAV viruses. We injected adult Nmu-Cre, CCK-Cre, Ntng1-Cre, VIP-Cre, Slc17a6-FlpO, and SST-FlpO mice with $3x10^{10}$-$1x10^{12}$ viral genomes of single or multiple AAVs each delivering fluorescent proteins after Cre- or FlpO-dependent recombination. Large volumes (mm^3) of tissue were optically cleared using either Ce3D or PEGASOS and imaged using a Nikon AXR laser scanning confocal microscope at spatial resolutions less than 1µm. Parsing multicolor labels, annotation, segmentation, and automatic feature extractions were performed by an in-house semi-automated human-in-the-loop neurite tracing software, which integrates advanced artificial intelligence (AI), machine learning, and graph-search algorithms for extraction of the single neuron as an object of actual labeling intensity. The software provides real-time visualization and user curation. Segmentation of tissue autofluorescence and registration onto tissue atlases allow the identified locations of neuronal processes to specific nuclei, ganglia or fiber tracts. Single-cell morphology data, including tissue-registered and AI-identified cell features, are databased with curated and clean metadata regarding the cell targeting approach with links to available single-cell expression atlases, facilitating the link between structure and function. Overall, the experimental workflow and data management strategy greatly increases throughput and objectivity in identifying single-neuron morphology, facilitating enhanced insights for the study of neuronal morphology and connectivity. Open Science availability of our software solutions should facilitate rapid morphological classification of transcriptionally distinct neurons throughout the nervous system. Supported by 5R01DK129315 and DP2AT010875.

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Poster

PSTR489: Sample Preparation and Novel Probes

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Topic: I.03. Anatomical Methods

Support: RF1MH120020
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GM127102
R24GM137200
U24NS120055
1S10OD021784
R01DA038896
NSF2014862-UTA20-000890

Title: Developing recombinant rabies viral vectors for multimodal and multiscale neural circuit mapping

Authors: *A. BOUIN[1,2], G. WU[3], Q. YE[4], T. C. HOLMES[5], M. ELLISMAN[6], X. XU[7];
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Abstract: New viral tools are critical for improving anatomical mapping and functional studies of cell-type-specific and circuit-specific neural networks in the intact brain. In our recently published study (Bouin *et al.*, 2024 Molecular Psychiatry), we report 20 new recombinant rabies virus (RV) vectors that we have developed for multi-scale and multi-modal neural circuit mapping tools. Our new RV tools for mesoscale imaging express a range of improved fluorescent proteins. Further refinements target specific neuronal subcellular locations of interest (nucleus, plasma membrane, somatodendritic, pre- and post-synaptic specializations and mitochondria). We demonstrate the discovery power of these new tools including the detection of detailed microstructural changes of rabies-labeled neurons in aging and Alzheimer's disease mouse models. We also have created recombinant RVs expressing red fluorescent and bioluminescent reporters. In addition, we have developed and tested RVs that encode GFP and ferritin as electron microscopy (EM) and fluorescence microscopy reporters for dual EM and mesoscale imaging. These new viral variants significantly expand the scale and power of rabies virus-mediated neural labeling and circuit mapping across multiple imaging scales in health and disease. A remaining challenge in the development of our novel RV tools is aimed at attenuating viral toxicity *in vivo*. We now make these powerful new tools available to the neuroscience community through our established service platform at the UC Irvine Center for Neural Circuit Mapping.

Disclosures: A. Bouin: None. **G. Wu:** None. **Q. Ye:** None. **T.C. Holmes:** None. **M. Ellisman:** None. **X. Xu:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR489.15/X11

Topic: I.03. Anatomical Methods

Support: NIH Grant R01MH130755

Title: Anatomical connectivity mapping of discrete lateral septum projection populations

Authors: *S. KARKARE[1], J. ISAAC[1], M. MURUGAN[2];
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Abstract: The lateral septum (LS) has been implicated in a wide range of behaviors, including aggression, reward processing, locomotion, feeding, and kin recognition. Yet, how the LS

contributes to such diverse behaviors is still unknown. Anatomically, the LS is positioned to route and modulate information from the hippocampus to various subcortical regions. However, the anatomical connectivity of the LS within the brain has never been systematically investigated using modern neuroscience techniques. This study aims to map six distinct lateral septum projection populations and explore how the whole brain inputs to these populations may vary. We first implemented a retrograde viral tracing strategy to identify the anatomical organization of projections from the LS to the nucleus accumbens (NAc), bed nucleus of the stria terminalis (BNST), ventromedial hypothalamus (vmH), basolateral amygdala (BLA), ventral tegmental area (VTA), and periaqueductal gray (PAG). We identified that LS neurons that project to each of these downstream regions occupy distinct subregions within the LS and are organized along the dorsoventral axis of the LS. We next determined monosynaptic inputs to each of the six projection populations using a modified glycoprotein-deleted retrograde rabies tracing strategy. Using a semi-automated whole brain segmentation and cell counting software, we quantified the input neurons to each projection population across the whole brain. We found largely overlapping input regions with some variance between hippocampal, thalamic, and hypothalamic inputs to each projection population. Similar levels of input from these regions could indicate an integration of information or neuromodulation at the level of the LS to modulate downstream behaviors mediated by the distinct projection populations. In the future, we aim to further understand the functional responses of each projection population.

Disclosures: S. Karkare: None. **J. Isaac:** None. **M. Murugan:** None.

Poster

PSTR489: Sample Preparation and Novel Probes

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The Yant Family Spinal Cord Injury Regeneration Fund (to AC Lepore)
Institutional Research Training Grant in Cellular, Biochemical and Molecular Sciences Grant T32GM144302NRSA

Title: An optimized method for isolating live, intact lower motor neurons from the adult mouse spinal cord that innervate defined muscle groups using retrograde tracing and fluorescence-activated cell sorting

Authors: *S. J. THOMAS[1], H. JAFRI[2], M. B. DALVA[3], A. C. LEPORE[2];
[1]Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Farber Inst. of Neurosci. Thomas Jefferson Univ., Philadelphia, PA; [3]Neurosci., Tulane Univ., New Orleans, LA

Abstract: We present a method to isolate specific populations of lower motor neurons innervating defined muscle groups from the adult mouse spinal cord by combining retrograde fluorescent neural tracing with fluorescence-activated cell sorting (FACS). Our approach overcomes long-standing challenges related to obtaining live primary spinal motor neurons and provides a powerful tool for studying these motor neurons in a targeted manner. We first inject a fluorophore-conjugated dextran amine tracer into specific muscles to label their corresponding motor neuron cell bodies in the ventral horn. The labeled spinal cord tissue is then dissociated into into a single-cell suspension using an optimized protocol that includes protease digestion, mechanical dissociation, a Percoll density gradient to enrich for neurons and remove myelin debris, and a Hibernate A medium supplemented with components to mitigate excitotoxicity and prevent cell swelling and/or death during sorting. Our usage of bright fluorescent tracers and live/dead markers allows us to cleanly gate and sort a pure population of live, intact lower motor neurons suitable for a wide range of downstream analyses, including proteomic and transcriptomic studies. This approach facilitates the study of spinal motor neurons within defined circuits, expanding our understanding of motor neuron biology and related pathologies.

Disclosures: S.J. Thomas: None. **H. Jafri:** None. **M.B. Dalva:** None. **A.C. Lepore:** None.

Poster

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NIH R35GM146973
Rita Allen Foundation GA_032522_FE
EMBO ALTF 874-2021
NSF GRF DGE 2036197

Title: Adeno-associated viral tools to trace neural development and connectivity across amphibians

Authors: E. C. B. JAEGER[1], D. VIJATOVIC[2], A. DERYCKERE[1], N. ZORIN[3], A. L. NGUYEN[4], G. IVANIAN[2], J. WOYCH[1], R. C. ARNOLD[2], A. ORTEGA GURROLA[1], A. SHVARTSMAN[3], F. BARBIERI[2], F. A. TOMA[2], H. T. CLINE[5], T. F. SHAY[6], D. B. KELLEY[1], A. YAMAGUCHI[4], M. SHEIN-IDELSON[3], M. TOSCHES[1], ***L. B. SWEENEY**[2]; [1]Dept. of Biol. Sci., Columbia Univ., New York, NY; [2]Inst. of Sci. and Technol. (ISTA), Klosterneuburg, Austria; [3]Dept. of Neurobio., Biochem. and Biophysics, Tel Aviv Univ., Tel Aviv, Israel; [4]Dept. of Biol., Univ. of Utah, Salt Lake City, UT; [5]Dept. of Neurosci. and Dorris

Neurosci. Ctr., The Scripps Res. Inst., La Jolla, CA; [6]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: The development, evolution, and function of the vertebrate central nervous system (CNS) can be best studied using diverse model organisms. Amphibians, with their unique phylogenetic position at the transition between aquatic and terrestrial lifestyles, are valuable for understanding the origin and evolution of the tetrapod brain and spinal cord. Their metamorphic developmental transitions and unique regenerative abilities also facilitate the discovery of mechanisms for neural circuit remodeling and replacement. The genetic toolkit for amphibians, however, remains limited, with only a few species having sequenced genomes and a small number of transgenic lines available. In mammals, recombinant adeno-associated viral vectors (AAVs) have become a powerful alternative to genome modification for visualizing and perturbing the nervous system. AAVs are DNA viruses that enable neuronal transduction in both developing and adult animals with low toxicity and spatial, temporal, and cell-type specificity. However, AAVs have never been shown to transduce amphibian cells efficiently. To bridge this gap, we established a simple, scalable, and robust strategy to screen AAV serotypes in three distantly-related amphibian species: the frogs *Xenopus laevis* and *Pelophylax bedriagae,* and the salamander *Pleurodeles waltl*, in both developing larval tadpoles and post-metamorphic animals. For each species, we successfully identified at least two AAV serotypes capable of infecting the CNS. In addition, we developed an AAV-based strategy that targets isochronic cohorts of developing neurons - a critical tool for parsing neural circuit assembly. Finally, to enable visualization and manipulation of neural circuits, we identified AAV variants for retrograde tracing of neuronal projections in adult animals. Our findings expand the toolkit for amphibians to include AAVs, establish a generalizable workflow for AAV screening in non-canonical research organisms, generate testable hypotheses for the evolution of AAV tropism, and lay the foundation for modern cross-species comparisons of vertebrate CNS development, function, and evolution.

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Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.01/X14

Topic: I.04. Physiological Methods

Support: Georgetown University Center for Neuro Engineering 2023 pilot grant

Title: A large number of neurons identified by calcium transients via pinhole illumination

Authors: C. LI[1], S. VICINI[2], *J.-Y. WU[3];
[1]Thomas Jefferson High Sch. for Sci. and Technol., Alexandria, VA; [2]Dept Pharmacol. & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [3]Neurosci., Georgetown Univ., Washington, DC

Abstract: Optical recording from large numbers of neurons is an indispensable technique for studying neuronal ensembles. We use optical sectioning through pinhole illumination to reduce the background fluorescence (F0) and increase the optical signal (dF/F0) in brain slices, allowing an ordinary fluorescent microscope to capture calcium transients from hundreds of CA1 neurons expressing GCaMP6f (Thy1-GCaMP6f) - a marked increase compared to ordinary wide-field fluorescent illumination, which can only detect calcium signals from a few neurons. Multiple layers of overlapping neurons can be identified by the spatial distribution of their dF/F0 amplitude (Figure 1). The illumination pinhole was created by closing the field diaphragm of the epi-illuminator of a microscope (Olympus BX51W), to block ~90% of the illumination light. The image of the pinhole was then projected onto the tissue by a 20X NA 0.95 water immersion objective (Olympus) to achieve optical sections ~100 um thick and excited by a 470nm LED (ThorLabs). Imaging was performed by an 80x80 CCD camera (NeuroCCD) at 125 frames/s. The signal-to-noise ratio was adequate (Figure 1C) even at the low excitation light level, allowing for a recording time of 3,000 seconds without significant bleaching. Putative CA1 pyramidal neurons fire at a low rate. Adding a low dose of 4-aminopyridine (~2 uM) increases the spontaneous firing rate and the probability of detecting neurons. A bright dF/F0 annulus surrounding the pinhole (Figure 1D, EPL) during an epileptiform event demonstrates that the enhancement of the dF/F0 is associated with the optical sectioning effect of the pinhole. The signal-to-noise ratio was high enough for an inexpensive 10-bit CMOS camera (e.g. Thorlabs CS135MU) to be used. Our method offers a simple and open-source tool for recording large numbers of neurons without the modification of ordinary fluorescent microscopes. We hope this low-cost method can be utilized by more neuroscientists interested in monitoring neuronal ensemble activity (Supported by Georgetown University Center for Neuro Engineering 2023 pilot grant).

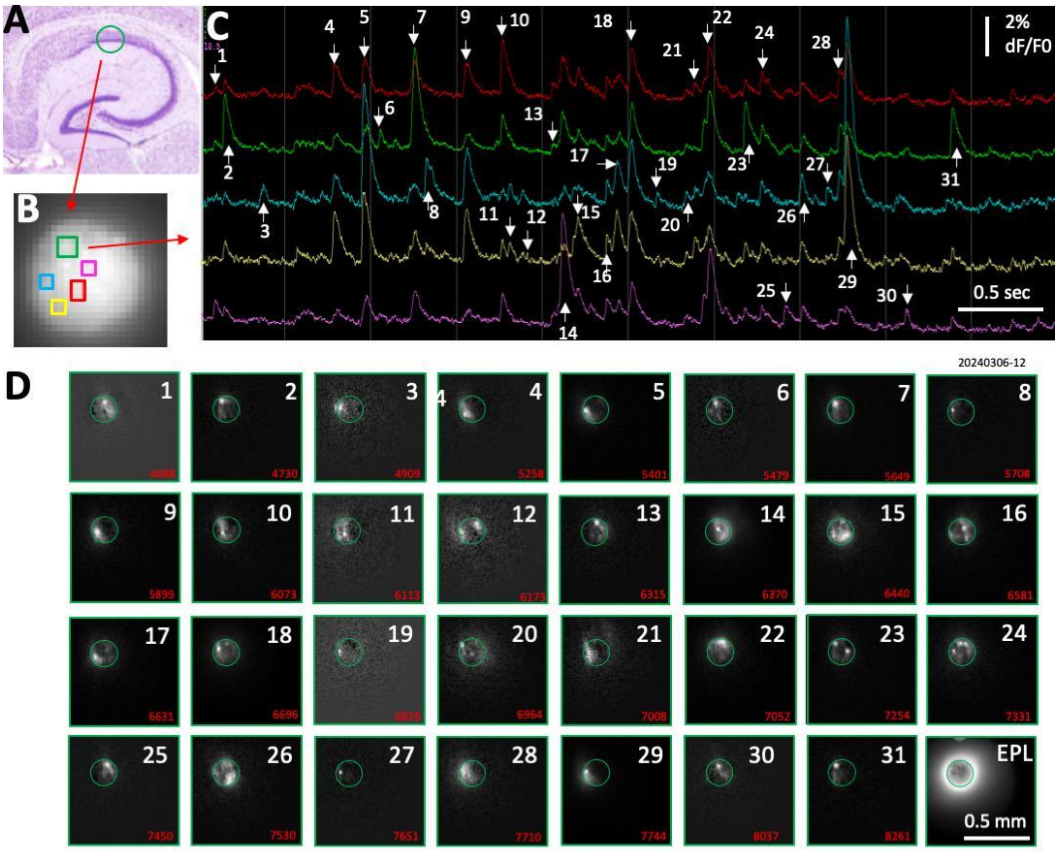

Figure 1. ***A.*** CA1 stratum pyramidale was imaged by the pinhole ***B.*** Five arbitrary ROIs were selected in the pinhole. ***C.*** The dF/F0 traces of the ROIs were plotted, showing Ca spikes. ***D.*** Image generated by subtracting the image at the dF peak, marked by white arrows in ***B,*** from the baseline image before each peak. ***EPL,*** an epileptiform event.

Disclosures: C. Li: None. **S. Vicini:** None. **J. Wu:** None.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.02/X15

Topic: I.04. Physiological Methods

Title: Application of a novel automated data analysis method for wide-field calcium imaging in the cortex of awake, head-fixed mice: preliminary assessment of the effects of a psychedelic compound on functional connectivity

Authors: *U. JULKU[1], R. LEVIN[1], D. TOPTUNOV[1], T. KOPCSANYI[1], P. WREN[2], T. RAY[2], **E. PRYAZHNIKOV**[1];
[1]Neurotar, Helsinki, Finland; [2]Mindstate Design Labs, South San Francisco, CA

Abstract: Wide-field calcium imaging is a valuable tool for studying cortex-wide neural activity in awake mice. In this study, we utilized Neurotar's proprietary Invigilo for wide-field imaging during active locomotion. The mice were head-fixed in an air-lifted platform where they could move in 2D or stay still at will. Invigilo's tracking software allowed segmenting imaging data into running versus resting states. The primary study objective was to develop an analysis methodology to quantify the impact of the psychedelic compound MSD-001 (5-MeO-MiPT) on cortical calcium activity and functional connectivity in awake mice. Eight GCaMP6s mice received a single oral dose of MSD-001 (5 mg/kg). We recorded calcium signals at baseline and continuously for 60 minutes post-treatment, as well as at matched times on days three and seven post-treatment. Our automated data analysis method incorporated noise reduction, hemodynamic signal correction, signal normalization, and background noise subtraction. It was superimposed on both running and resting sub-sets of the imaging data. Functional clusterization was performed for each mouse separately. To compare baseline and post-dosing results across the cohort, we analyzed geometrically overlapping clusters for all mice and created heat maps and images for visualization. Segmentation into running vs. resting states allowed us to distinguish locomotion effects from treatment-induced changes. Running evoked notable increases in calcium activity and functional connectivity in all cortical areas. In the resting state, we observed both acute and sustained increase in calcium activity in somatosensory and motor cortices and functional connectivity in most of the cortical areas after MSD-001 treatment. In the running state, such effects were mainly apparent in the visual cortex albeit against a higher baseline of calcium activity. Thus, MSD-001 had both acute and long-term effects on calcium signaling and functional connectivity in the mouse cortex, but additional vehicle-controlled studies are required to confirm the specific effects of MSD-001. The new analysis method allowed us to analyze longer epochs (up to one hour) than in the previous studies (Shahsavarani *et al*, Cell Rep 2023; West *et al*, Cereb Cortex 2022), segment the imaging data based on locomotor activity, and distinguish between calcium changes resulting from locomotion versus from a therapeutic intervention. The method offers a robust framework for studying cortical calcium activity and functional connectivity *in vivo* in the context of preclinical drug development.

Disclosures: U. Julku: A. Employment/Salary (full or part-time):; Neurotar. **R. Levin:** A. Employment/Salary (full or part-time):; Neurotar. **D. Toptunov:** A. Employment/Salary (full or part-time):; Neurotar. **T. Kopcsanyi:** A. Employment/Salary (full or part-time):; Neurotar. **P. Wren:** A. Employment/Salary (full or part-time):; Mindstate Design Labs. **T. Ray:** A. Employment/Salary (full or part-time):; Mindstate Design Labs. **E. Pryazhnikov:** A. Employment/Salary (full or part-time):; Neurotar.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

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Program #/Poster #: PSTR490.03/X16

Topic: I.04. Physiological Methods

Support: NIH Grant 4R44MH132234-02

Title: Rapid Volumetric Brain Imaging by Spatiotemporal Axial Beam Multiplexing

Authors: G. JAINDL[1], A. VAZIRI[2], ***D. PERUZZI**[3], J. GLASER[1];
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Abstract: Standard two-photon scanning microscopy techniques for brain imaging often face challenges in balancing image resolution, acquisition speed, and signal-to-noise ratio (SNR). These challenges become particularly pronounced during volumetric imaging due to the light-scattering properties of brain tissue. Light Beads Microscopy (LBM) provides a solution to these challenges by optimizing spatiotemporal signal acquisition to record data at rates limited by the fluorescence lifetime of neural calcium indicators, such as GCaMP. LBM leverages high-energy femtosecond laser pulses at a relatively low repetition rate (~4.5 MHz to 5 MHz) to enable the highly temporally multiplexed acquisition of up to 30 axial planes within the same timeframe required for traditional two-photon microscopy to capture a single plane. Additionally, LBM enhances SNR by utilizing one excitation pulse per voxel. In recent studies, LBM, used in conjunction with a mesoscope, has demonstrated the ability to record the calcium dynamics of approximately one million neurons at 2 Hz within a volume of approximately 5.4 × 6 × 0.5 mm in the mouse brain cortex. This breakthrough promises new avenues for exploration in mammalian brain research. Here, we describe a new LBM system that optimizes and streamlines the light beads implementation by improving its stability, while reducing its footprint and alignment complexity. We also demonstrate integrating LBM into a standard open-source two-photon scanning microscope. This effort aims to broaden accessibility to LBM technology within the neuroscience community, facilitating further innovation and discovery in the field.

Disclosures: G. Jaindl: A. Employment/Salary (full or part-time):; MBF Bioscience. **A. Vaziri:** None. **D. Peruzzi:** A. Employment/Salary (full or part-time):; MBF Bioscience. **J. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

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Topic: I.04. Physiological Methods

Support: K25AG086674

Title: Neuronal signaling using live cell light sheet imaging with low and high spatial coherence detection

Authors: *M. POTCOAVA[1], Z. ZURAWSKI[1], L. M. TAI[1], K.-Y. TSENG[1], C. MANN[2], S. T. ALFORD[1];
[1]Dept of Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL; [2]Dept of Applied Physics and Materials Sci., Northern Arizona Univ., Flagstaff, AZ

Abstract: Neurons are complex 3-dimensional (3D) structures adapted for rapid signaling. Signaling is mediated by neurotransmitter, hormonal, and second messenger systems highly localized to specific sites of activity which are released, bind, and inactivate in times scales of milliseconds or less. Many fluorescent probes and genetically engineered sensors have been developed to investigate these signals, but imaging systems that utilize these probes and resolve data in 3 dimensions pose problems for live cell real time imaging. These problems include slow scanning, photobleaching and limited resolution. It is also valuable to combine imaging modalities with electrophysiological recording of neurons and glia, but lens movement needed to generate volume resolved imaging can be challenging. Lattice Light Sheet (LLS) Imaging can resolve some of these issues. The approach generates high resolution in x, y and z axis, and suffers very little photobleaching but requires simultaneous movement of the lattice sheet position and objective lens. We developed an LLSM configuration based on the Janelia Research design for *in situ* recording that allows simultaneous electrophysiological recording. We have used LLS to assess neuron structure and synaptic function *in situ*. We will demonstrate use of the LLSM to measure stimulus-evoked localized Ca^{2+} entry. We also demonstrate resolution of Ca^{2+} signaling in single synapses alongside the 3D structure of those synapses. A challenge in 3D imaging is the need to move the emission objective to maintain focus. Phase imaging of live cells and tissue opens several possibilities that have not been available to more established methods in microscopy. The simplest example is the ability of holographic imaging to reconstruct 3-dimensional information by both effectively autofocusing and extending the depth of field from which valuable information can be gathered. We have developed an incoherent holographic lattice light-sheet (IHLLS) technique to replace the LLS tube lens with a dual diffractive lens to obtain 3D images of spatially incoherent light diffracted from an object as incoherent holograms. 3D structure is reproduced within the scanned volume without moving the emission objective. This eliminates mechanical artifacts and improves temporal resolution. We focus on LLS and IHLLS applications and data obtained in neuroscience and emphasize increases in temporal and spatial resolution using these approaches.

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Poster

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Topic: I.04. Physiological Methods

Support: NIH Grant U01NS113273
NIH Grant 1R01EY033950

Title: High performance multiphoton imaging with large area SiPMs

Authors: *D. PETERKA[1], T. S. MIHAILA[2], E. LIESER[4], J. ORACH[4], B. RADTKE[4], A. LOSONCZY[3], J. BROOKER[4];
[1]Zuckerman Mind Brain Behavior Inst., [2]MD/PhD Program, Columbia Univ., New York, NY; [3]Neurosci., Columbia Univ., Westport, CT; [4]Thorlabs Inc., Sterling, VA

Abstract: Multiphoton Imaging has become a mainstay in neuroscience for its cellular resolution, optical sectioning, and penetration depth. This technique usually relies on photomultiplier tubes for fluorescence detection because of their low noise, high sensitivity, and high gain. Unfortunately, this high sensitivity comes with a cost - these detectors are very sensitive to ambient light, and can be easily damaged when paired with optogenetic activation or the presentation of visual stimuli. Silicon photomultiplier arrays offer similar sensitivity, and much greater damage resistance, but they typically suffer from much higher baseline dark counts than PMTs, especially for large area arrays, precisely the kind that are needed for deep imaging. Here we describe the performance of a large-area deeply cooled SiPM array, with significantly lower baseline dark counts, near immediate recovery from external light, and high sensitivity. We demonstrate its effectiveness in a variety of functional imaging contexts, combining imaging with photostimulation or visual stimulations, and highlight its unique capabilities for imaging in lit environments.

Disclosures: D. Peterka: None. **T.S. Mihaila:** None. **E. Lieser:** A. Employment/Salary (full or part-time):; Thorlabs Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Thorlabs Inc. **J. Orach:** A. Employment/Salary (full or part-time):; Thorlabs Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Thorlabs Inc. **B. Radtke:** A. Employment/Salary (full or part-time):; Thorlabs Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Thorlabs Inc.. **A. Losonczy:** None. **J. Brooker:** A. Employment/Salary (full or part-time):; Thorlabs Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Thorlabs Inc..

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.06/X20

Topic: I.04. Physiological Methods

Support: FY24 McDonnell Center for Systems Neuroscience Small Grant

Title: Three-dimensionally resolved, high-density neural recording using PRIME: a novel single fiber photometry approach

Authors: *S. YANG[1], K. YANG[2], K. MARDANI[3], Q. CHEVY[2], S. JI[1], J. HAN[1], A. KEPECS[2], S. HU[1];
[1]Dept. of Biomed. Engin., [2]Neurosci., [3]Dept. of Electrical and Syst. Engin., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Fiber photometry has revolutionized neuroscience research by enabling simple yet effective recording of various neural activities *in vivo*, including the calcium dynamics of diverse neuronal types and the release of neuromodulators and neurotransmitters. However, conventional fiber photometry, which confines the recording to a small and fixed brain region near the fiber tip, faces significant limitations including the limited recording volume and the lack of spatial resolution. Recent advances in fiber photometry based on tapered fibers and multi-fiber implantation, although promising, only partially address these constraints. In this work, we extend our newly developed PRIME (**P**anoramically **R**econfigurable **I**llu**M**inativ**E**) technique from optogenetic stimulation to photometric recording. This new design features a single implant with 3,000 independently addressable light emitters and collectors that span 4.5 mm axially and 360° axially over a 200-μm, conical-shaped, laser-engineered fiber. Further, we have supplemented the bi-directional PRIME fiber with a head-mounted device and a signal-processing strategy to mitigate artifacts induced by animal movement, light fluctuation, and autofluorescence. We demonstrated the utility of this new technology by mapping dopamine dynamics in the striatum of awake mice, where we observed spatially distinct dopamine dynamics across the dorsal-ventral axis with higher dopamine release in the ventral striatum during reward retrieval. Our results demonstrate the promise of the PRIME fiber photometry as an enabling tool for large-scale, high-density, spatiotemporal mapping of neural activities in behaving animals through a single fiber.

Disclosures: S. Yang: None. **K. Yang:** None. **K. Mardani:** None. **Q. Chevy:** None. **S. Ji:** None. **J. Han:** None. **A. Kepecs:** None. **S. Hu:** None.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

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Program #/Poster #: PSTR490.07/X21

Topic: I.04. Physiological Methods

Support: STI2030-Major Projects2021Z(D0204503)
National Natural Science Foundation of China (32125020)
China Postdoctoral Science Foundation (2023M743609)
National Natural Science Foundation of China (32300936)

Title: Volumetric Voltage Imaging with Confocal Light Field Microscope

Authors: *L. BAI[1], L. CONG[1], Z. SHI[1,2], Y. ZHAO[1,2], Y. ZHANG[1], B. LU[1], J. ZHANG[1], Z.-Q. XIONG[1], N. XU[1], Y. MU[1], K. WANG[1,2,3];

[1]Inst. of Neurosci., CAS, Shanghai, China; [2]University of Chinese Academy of Sciences, Beijing, China; [3]ShanghaiTech University, Shanghai, China

Abstract: Voltage imaging is an emerging optical imaging technique that employs voltage-sensitive probes to monitor neuronal membrane potential changes. By combining the advantages of electrophysiology and optical imaging, voltage imaging is poised to become one of the most promising tools in neuronal activity recording. However, volumetric voltage imaging still faces several challenges. Firstly, due to the rapid changes in neuronal voltage signals, the imaging system must strike a balance between imaging speed and imaging volume to effectively capture these signals. Secondly, voltage probes exhibit weak fluorescence intensity and limited dynamic range, requiring the imaging system to have a higher signal-to-noise ratio to accurately detect and record the voltage changes.Current voltage imaging methods, such as wide-field and two-photon imaging, each present unique advantages but also face certain challenges in their application. Wide-field imaging is not constrained by the speed-volume trade-off but may encounter difficulties in achieving high signal-to-noise ratio, optical sectioning capability, and deep tissue imaging. Two-photon imaging provides excellent performance but may be limited in its ability to capture fast, large-volume neural network dynamics due to its serial scanning mechanism.To overcome these challenges, we explored the use of light field microscopy for three-dimensional (3D) voltage imaging. By optimizing the system design, our approach overcame the constraints in speed and noise performance, enabling long-term volumetric voltage imaging. This 3D imaging capability provides several advantages over traditional two-dimensional (2D) methods. It enables the simultaneous recording of neuronal activity across multiple layers of the cortex, revealing complex 3D neural coordination patterns that would be difficult to discern with 2D imaging. Furthermore, volumetric imaging allows for a more comprehensive understanding of the spatial organization and functional dynamics of neural networks in the brain.With this method, we successfully recorded spiking neurons in the mouse cortex and mapped 3D neural coordination patterns in the awake mouse brain. Our advancements present a robust method for routine volumetric voltage imaging, providing a valuable tool for studying neural dynamics at a larger scale and offering new insights into the 3D functional architecture of the brain.

Disclosures: L. Bai: None. **L. cong:** None. **Z. Shi:** None. **Y. Zhao:** None. **Y. Zhang:** None. **B. Lu:** None. **J. Zhang:** None. **Z. Xiong:** None. **N. Xu:** None. **Y. Mu:** None. **K. Wang:** None.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

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Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.08/X22

Topic: I.04. Physiological Methods

Support: 1RF1MH126882-01A1

Title: A scalable approach for mapping transcriptomically defined local circuits

Authors: *W. CUNNINGHAM[1], M. MOYA[2], M. ECONOMO[2];
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Abstract: The recent surge of transcriptomic atlasing data and projects in neuroscience have revealed the rich diversity and high specificity of cell types in neural circuits. Characterizing this architecture at the resolution of individual cells remains a formidable challenge due to the lack of scalable methods. By combining targeted optogenetic stimulation of individual cells with simultaneous voltage recordings, we aim to measure connections between pairs of neurons with a throughput 1,000 times greater than previously possible. Importantly, the all-optical basis of this method allows us to readily integrate synaptic connectivity measurements with highly multiplexed fluorescence in situ hybridization, allowing us to correspond cell type identity and circuit structure. Here, we showcase a proof-of-concept of this local synaptic mapping technique (LOCAL-SYNMAP) in the motor cortex, providing a framework for performing high-throughput connectivity mapping for any local circuit. Applying SYNMAP to capture large datasets promises to further our grasp of the brain's intricate structure, revealing how specific cell types comprise the functional circuits fundamental to cognition, learning, memory, and behavior.

Disclosures: W. Cunningham: None. **M. Moya:** None. **M. Economo:** None.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.09/X23

Topic: I.04. Physiological Methods

Support: NIH Grant EY028381
NIH Grant MH118928

Title: Pixel-wise programmability enables dynamic high-SNR cameras for voltage imaging and high-speed microscopy

Authors: *J. ZHANG[1], J. P. NEWMAN[1], Z. WANG[1], Y. QIAN[2], P. A. FELICIANO[1], W. GUO[3], T. HONDA[4], Z. CHEN[5], C. LINGHU[2], E. S. BOYDEN[1], M. A. WILSON[6];
[1]MIT, Cambridge, MA; [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]The Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [4]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [5]NYU Grossman Sch. of Med., New York, NY; [6]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: High-speed wide-field fluorescence microscopy has the potential to capture biological processes with exceptional spatiotemporal resolution. However, conventional cameras suffer from low signal-to-noise ratio (SNR) at high frame rates, limiting their ability to detect faint fluorescent events. Here, we introduce an image sensor where each pixel has individually programmable sampling speed and phase, so that pixels can be arranged to sample simultaneously at temporal resolution with a high SNR.

In high-speed voltage imaging experiments, by arranging neighboring pixels' exposure at different phase offsets, our image sensor increases the temporal resolution at sampling fast fluorescence events without increasing each pixel's sampling rate. The use of long exposure also increases the output SNR. Compared with a commercial low-noise sCMOS camera, our camera yields ~2-3 folds SNR improvement for the same temporal resolution. This SNR gain enables the detection of weak neuronal action potentials and subthreshold activities missed by the standard sCMOS cameras.
The pixel-wise programmable exposure (PE-CMOS) image sensor is fabricated in a 180 nm CMOS process, featuring a pixel pitch of 10 μm, high conversion gain (110 μV/e^-), high photodiode fill factor (75%), and supports a temporal resolution of 1040 Hz. Its CMOS-based design offers scalability to higher pixel numbers and speed to meet the demands of various imaging applications. The power efficiency, resulting from its ability to achieve high temporal resolution with low sampling speed, also makes it suitable for miniaturized head-mounted microscopes to enable kHz voltage imaging from freely moving animals and allow direct *in vivo* imaging of neural voltage activity to investigate fast-spiking activities underlying complex behavior.

Disclosures: J. Zhang: None. **J.P. Newman:** None. **Z. Wang:** None. **Y. Qian:** None. **P.A. Feliciano:** None. **W. Guo:** None. **T. Honda:** None. **Z. Chen:** None. **C. Linghu:** None. **E.S. Boyden:** None. **M.A. Wilson:** None.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

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Program #/Poster #: PSTR490.10/X24

Topic: I.04. Physiological Methods

Support: R44NS125689
R44NS132679

Title: Genomic Positioning System (GPS): High-resolution, high throughput electrophysiology integrated with AI/ML to map diseases, targets, and drugs for CNS therapeutic discovery

Authors: *J. FINK;
Quiver Biosci., Cambridge, MA

Abstract: The application of artificial intelligence (AI)/machine learning (ML) to biology, coupled with the complexity of the central nervous system (CNS), provides an opportunity to leverage new tools and ultra-large datasets to elucidate the pathophysiology of CNS disease and identify therapeutics. This approach is starting to be realized with single-cell RNA sequencing and morphometrics but has not yet been applied to the fundamental output of neurons, synaptic transmission and action potential firing, largely due to the lack of techniques that provide both the required scale and information content. Our solution is the Genomic Positioning System

(GPS), a platform that bridges high-resolution, high throughput electrophysiological mapping with AI/ML computation. Our method combines genetically encoded voltage sensors and actuators with specially designed instruments that record the electrical activity of individual human induced pluripotent stem cell (iPSC)-derived neurons with single neuron, single action potential resolution, in high throughput formats (500,000 neurons per day per instrument). The GPS allows for the rapid creation of information-rich datasets of unique neuronal activity patterns across diseases, genetic perturbations, and drug treatments.To date, we have applied the GPS platform to map several CNS diseases, including Fragile X Syndrome (FXS), Rett Syndrome, Dup15q syndrome, and various epileptic encephalopathies. Here we present the application of the GPS to FXS (paper under review), where we have identified a multiparameter hyperexcitable neuronal phenotype using ML-powered feature selection from different FXS patient samples and have validated our findings via rescue of our disease signature by (a) selectively reintroducing the FMR1 gene and (b) modifying neuronal networks via co-cultures with wild-type neurons. Our findings are consistent with literature reports but identify previously unseen electrophysiological features associated with FXS. We have further demonstrated through small molecule screening the ability to reverse key features of the multiparameter phenotype. We are now using the GPS to scale from studying one disease at a time to hundreds of diseases in parallel by performing a whole-genome CRISPR screen to establish electrophysiological signatures of 18,000 genetic targets. In parallel, we are building a library of signatures across 3,000 compounds to match drug mechanisms to disease rescue. Our approach highlights the application of the GPS for both elucidating disease biology and exploring diverse therapeutic approaches using unique data sets of neuronal physiology with advanced computation.

Disclosures: J. Fink: A. Employment/Salary (full or part-time):; Quiver Bioscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Quiver Bioscience.

Poster

PSTR490: Advanced Optical Methods for Fast Functional Imaging

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR490.11/X25

Topic: I.04. Physiological Methods

Support: FAER 230444-01

Title: Comparative Analysis of 405 nm Illumination and 530 nm Light Scattering Methods for Distinguishing Hemodynamic from Neural Signals in GCaMP Imaging

Authors: S. WU[1,2], ***J.-Y. LIOU**[3], T. H. SCHWARTZ[1], H. MA[1];
[1]Neurolog. Surgery, Weill Cornell Med., New York, NY; [2]Department of Neurosurgery, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, Wuhan, China; [3]Cornell University: Weill Cornell Med. Col., New York, NY

Abstract: Background: Genetically encoded calcium indicators like GCaMP are indispensable for monitoring neural activity via fluorescence imaging, but changes in hemodynamics often compromise their accuracy. The classical Beer-Lambert law-based approach uses 530-nm illumination to separate neural signals from hemodynamic artifacts by estimating changes in blood volume. In contrast, 405 nm illumination has recently gained popularity for its ability to induce calcium-insensitive fluorescence, providing potential optical discrimination between neural and hemodynamic activity. However, 405 nm photons may activate additional fluorophores that contribute to background noise, and the optical properties of 405 nm photons differ significantly from those at 470 nm, including a higher absorption coefficient by hemoglobin and stronger tissue scattering, potentially influencing the amplitude of recorded hemodynamic changes. These factors raise concerns about the accuracy of the 405-nm isosbestic method compared to the established 530-nm light scattering method. Objective: To evaluate and compare the effectiveness of 405 nm and 530 nm illumination methods in reducing hemodynamic artifacts in GCaMP-based fluorescence imaging of neuronal activity. Methods: We conducted widefield epifluorescence imaging experiments in two GCaMP6f-expressing mouse lines over the cortex, targeting different neuronal populations: Thy1-GCaMP6f (Kim 5.5), which labels deep cortical neurons, and rasgrf2-GCaMP6f, primarily labeling Layer 2/3 neurons. This approach allowed us to evaluate the impact of signal depth on the results. Serial images were acquired sequentially at 120 frames per second using 405-nm, 470-nm, and 530-nm illumination. We implemented two hemodynamic-signal separation protocols: the standard 530 nm light scattering method and the novel 405 nm illumination method under various scenarios. Results: The 405-nm isosbestic method consistently overestimated hemodynamic components in recordings from Thy1-GCaMP6f mice. Conversely, in the rasgrf2-GCaMP6f line, the 405-nm induced fluorescence underestimated hemodynamic changes, leading to insufficient hemodynamic subtraction. A linear regression method was developed to adjust the amplitude of the 405-nm data, achieving a hemodynamic-free calcium imaging dataset. Conclusion: Despite its popularity and simplicity, the 405 nm illumination method may not accurately separate neural and hemodynamic signals. Statistical calibration techniques can enhance the reliability of fluorescence imaging as a tool for studying dynamic neuronal processes.

Disclosures: S. wu: None. **J. Liou:** None. **T.H. Schwartz:** None. **H. Ma:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR491.01/X26

Topic: I.04. Physiological Methods

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BRAIN Initiative Grants RF1NS113287
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Minnesota Robotics Institute (MnRI)

MnDRIVE RSAM
The McKnight Foundation
UMN Mechanical Engineering Department
UMN Interdisciplinary Doctoral Fellowship

Title: Robotic-2p: a robotically actuated microscope for advanced two-photon imaging in freely locomoting mice

Authors: *P.-H. CHENG[1], D. FARINELLA[2], J. HOPE[1], J. GABLE[2], H. JAYAKUMAR[2], T. BECKERLE[1], Z. VIAVATTINE[1], A. KERLIN[2], S. KODANDARAMAIAH[1];
[1]Mechanical Engin., [2]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Computations in the brain involve dynamics across many anatomical and spatial scales - from integration at individual synapses to brain-wide neuromodulatory shifts. Studying these computations under naturalistic experimental conditions is critical to ensure that the networks under study are operating in dynamical regimes shaped by millions of years of evolution, rather than perturbed regimes they would never naturally visit. High-resolution imaging technologies, such as multiphoton imaging, have revolutionized systems neuroscience by allowing simultaneous recording and manipulation of brain activity at different scales. However, traditional microscopy techniques require unnatural head fixation, limiting the study of natural motor, self-motion, and sensory-spatial interactions. Miniaturized imaging devices have been developed to address this limitation, but these compromise performance and are incompatible with many advanced 2P imaging techniques.
Recently, we developed a cranial exoskeleton that enables mice to maneuver a neural recording headstage containing imaging devices up to 1.5 kg while navigating behavioral environments (Hope et al. Biorxix 2023). Building on this, we developed an exoskeleton for mice to maneuver a 2P imaging headstage around physical spaces robotically. This Robotic-2P microscope can move with the mouse to image the brain's neural activity and study complex behaviors of freely moving mice. This system offers a 4.5x improvement in payload capacity, supporting imaging devices weighing at least 7 kg. The system's headstage includes force sensors to detect milli-Newton scale forces the mouse applies to control the robotic platform's x, y, and yaw motion via an admittance controller. Optimized controller tuning parameters enable mice to locomote at velocities and accelerations similar to untethered control mice. We demonstrate mice maneuvering a headstage weighing 7 kg and navigating 2D arenas with locomotion performance similar to free behavior. Robotic-2P provides a flexible platform for neural recording of large payloads while exploring physical spaces, unveiling brain-wide mechanisms controlling complex behavior.

Disclosures: P. Cheng: None. **D. Farinella:** None. **J. Hope:** None. **J. Gable:** None. **H. Jayakumar:** None. **T. Beckerle:** None. **Z. Viavattine:** None. **A. Kerlin:** None. **S. Kodandaramaiah:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of Objective Biotechnology Inc..

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR491.02/X27

Topic: I.04. Physiological Methods

Support: NIH R01NS111028
RF1NS113287
1RF1NS126044
P30DA048742
The McKnight Foundation

Title: Mesoscale cortex-wide optical imaging of calcium dynamics in free behaving mice through an intact skull using a miniaturized wide-field imaging microscope

Authors: *K. SAXENA, D. A. SURINACH, S. FAUSNER, E. KO, S. B. KODANDARAMAIAH;
Mechanical Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Brain imaging at a mesoscale level in conjugation with genetically encoded calcium indicators, such as GCaMP, has become a state of the art tool for studying cortex-wide functional dynamics. In general, these studies are limited to head-fixed imaging or small field of view imaging during natural behaviors due to limitations in miniaturization technologies. We have previously used the mini-mScope, a head-mounted fluorescence microscope that allows cortex-wide calcium imaging in free behaving rodents (Rynes* Surinach et al Nat Methods 2021). Mini-mscope imaging was demonstrated to work through implantation of a transparent polymer skull across the dorsal cortex, which is a particularly challenging surgical procedure. To mitigate this issue, we have developed a transparent skull preparation that leverages refractive index matching to image through the intact skull in mice using the mini-mScope. The optimized preparation can be done in < 20 minutes. By utilizing this preparation, we have performed wide-field calcium imaging in mice using the mini-mScope without the need for a craniotomy. We have compared the signal-to-noise ratio for the transparent skull preparation compared to a cranial window implantation and have found the quality of the signals to be similar for mesoscale imaging during spontaneous open-field behavior. Additionally, we have performed visual stimulus to both groups to perform cortical sensory mapping during awake, freely behaving mice.

Disclosures: K. Saxena: None. **D.A. Surinach:** None. **S. Fausner:** None. **E. Ko:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

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Program #/Poster #: PSTR491.03/X28

Topic: I.04. Physiological Methods

Support: NIH R01NS111028
RF1NS113287
1RF1NS126044
P30DA048742
The McKnight Foundation

Title: Computer vision guided open source active commutator for neural imaging in freely behaving animals

Authors: *I. OLADEPO, K. SAXENA, D. A. SURINACH, M. LEHMAN, S. B. KODANDARAMAIAH;
Mechanical Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: Miniaturized neural interfaces are essential for probing the neural dynamics underlying animal behavior, and often require a wired connection with slip rings to mitigate wire twisting and torsional stress. The push for continuous, long-term neural recording has prompted the creation of active commutators that can autonomously manage wire twisting by sensing animal pose changes and adjusting the slip ring's orientation. Current solutions however require addition of sensing modules and are limited to heading angle compensation alone. Here we developed a computer vision (CV) guided active commutator that employs CV algorithms (DeepLabCut) for real-time tracking of animal position and orientation to dynamically control the slip ring, thus compensating for changes in the animal's heading angle and position.To show that CV guided active commutation does not affect measured neurophysiological signals, we performed cortex-wide mesoscale calcium imaging using a miniaturized imaging device (mini-mScope). We were able to stably record Calcium dynamics at 30 frames per second, with only 25 frames dropped during a recording lasting 10 minutes (0.13% of a total of 18,000 frames). Qualitatively, the recorded Calcium activities in the regions of interest distributed throughout the cortex were similar to those acquired without active commutation.This system has been extensively tested in three different behavioral tasks, demonstrating its capability to facilitate stable, uninterrupted widefield cortical imaging in mice.

Disclosures: I. Oladepo: None. **K. Saxena:** None. **D.A. Surinach:** None. **M. Lehman:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

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Support: UMN Mechanical Engineering Department
MnDRIVE RSAM
The McKnight Foundation
Minnesota Robotics Institute (MnRI)
NIH grant 1R01NS11128
Brain Initiative grant RF1NS113287
Brain Initiative grant RF1NS126044

Title: Brain-wide, multi-site, multi-day high-density electrophysiology recordings in mice navigating physical spaces

Authors: *T. BECKERLE[1], M. FELDKAMP[2], J. HOPE[2], R. CARTER[3], T. J. EBNER[3], S. B. KODANDARAMAIAH[2];
[1]Univ. of Minnesota, Minneapolis, MN; [2]Mechanical Engin., Univ. of Minnesota, Minneapolis, MN; [3]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Complex behaviors are mediated by neural computations occurring throughout the brain. In recent years, multi-site Neuropixel recordings have enabled the study of large populations of neurons in rodents. But most of these studies have been confined to simple head fixed tasks, owing to the weight of not only the probes, but the peripheral hardware such as the motorized stages used to lower the Neuropixels into the brain. To mitigate this issue, we have recently developed an exoskeleton assist for mice that allow mice to locomote naturally, while maneuvering headstages that are orders of magnitude larger and heavier than themselves through physical spaces (Hope et al Biorxiv 2023). We leverage the exoskeleton to develop a compatible headstage that can simultaneously lower up to 4 Neuropixels into the brain for recording from distributed sites in the brain, while also monitoring behavior of the animal using an onboard behavior camera. We established an optimized protocol for multi-site, multi-day Neuropixel probe insertions that allow simultaneous recordings, bilaterally from the prefrontal cortex, primary somatosensory cortex, and hippocampus brain regions. We present data on simultaneous neuropixel recording in mice navigating a physical 8 maze arena. These preliminary results pave the way for future studies where brain wide recordings using high-density Neuropixel probes are possible in complex behaviors that cannot currently be studied in headfixed animals.

Disclosures: T. Beckerle: None. **M. Feldkamp:** None. **J. Hope:** None. **R. Carter:** None. **T.J. Ebner:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

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Topic: I.04. Physiological Methods

Support: BRAIN Initiative grant RF1NS113287
BRAIN Initiative grant RF1NS126044
McKnight Foundation
MN Robotics Institute

Title: Distributed encoding of space in neural populations across the dorsal cortex

Authors: *M. K. FELDKAMP[1], J. HOPE[1], R. PETERS[2], T. BECKERLE[1], A. D. REDISH[3], S. B. KODANDARAMAIAH[4];
[1]Mechanical Engin., Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Minneapolis, MN; [3]Dept. Neurosci, Univ. of Minnesota, Minneapolis, MN; [4]MECHANICAL Engin., Univ. Of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Navigation is a fundamental behavior necessary for survival. The neuronal computations mediating spatial navigation may be distributed throughout the brain, and interrogation of these neural activities simultaneously during spatial navigation tasks have been challenging. We previously developed a robotic cranial exoskeleton capable of supporting the weight of neural recording hardware orders of magnitude heavier and larger than a mouse while still allowing mice to move through a physical space (Hope et al BioRxiv 2023). We utilized the cranial exoskeleton equipped with a wide-field neural imaging macroscope to record single-cell neural dynamics of over 30mm2 of the dorsal cortex when mice were navigating an 8-maze arena (n = 7 mice, 12 to 14 recording sessions in each mouse across 47 days). Neural recordings were obtained across the visual, somato-sensory, retro-spenial, motor and association cortices. In total, we recorded over 24,500 cells with ~80% of these cells tracked across multiple sessions. Preliminary analysis of this large-scale dataset revealed distributed populations of the neurons throughout the cortex that encode spatial locations, with an average of ~37 % of cells meeting the criteria for place encoding, with higher concentrations of spatially tuned cells in the medial and posterior regions of the cortex. Characterizing the change of single-cell place-tuning across multiple sessions, we find that in earlier sessions the neural encodings are less consistent, but that in later sessions these encodings shift towards a more consistent representation of space and stabilize over time. Cranial exoskeleton assists can thus be used to obtain largescale, multi-session neural recordings during complex tasks such as spatial navigation of physical spaces.

Disclosures: M.K. Feldkamp: None. **J. Hope:** None. **R. Peters:** None. **T. Beckerle:** None. **A.D. Redish:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

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Program #/Poster #: PSTR491.06/X31

Topic: I.04. Physiological Methods

Support: NIH R21EY029472
NSF 1847141
Burroughs Wellcome Fund CASI 1015761

Title: Miniaturized Lensless Microscope for Recording Neural Activity in vivo

Authors: F. TIAN, B. MATTISON, ***W. YANG**;
Univ. of California Davis, Davis, CA

Abstract: Miniaturized fluorescence microscopes are powerful tools for bio-imaging applications which necessitate a compact device footprint and lightweight design. One important application is head-mounted microscopes for imaging neural activity in freely-behaving animals. Conventional one-photon miniaturized microscopes with an objective lens and a tube lens have a general tradeoff among device footprint, field of view, and imaging. Moreover, there is a lack of 3D imaging and resolving capability. The advent of lensless microscopes overcome these limitations by replacing bulky optics with a thin optical mask placed close to the camera, significantly reducing the thickness and enabling the capture of 3D data on a 2D plane. However, the technology faces challenges in high-quality image retrieval and computationally efficient inverse imaging algorithms. Here we develop a miniaturized lensless microscope with custom-designed doublet microlens array, and a multi-stage physics-informed deep learning model that dramatically saves the computational resources and enables real-time, high-quality 3D reconstruction. This device has a field of view ~4×6 mm^2, a lateral resolution ~10 μm and an axial resolution ~50 μm. We demonstrated in vivo calcium imaging of awake mouse in visual cortex with cellular resolution. Our miniaturized lensless microscope holds great promise to image neuronal activity over a large volume in freely-behaving animals.

Disclosures: F. Tian: A. Employment/Salary (full or part-time):; University of California, Davis. **B. Mattison:** A. Employment/Salary (full or part-time):; University of California, Davis. **W. Yang:** A. Employment/Salary (full or part-time):; University of California, Davis.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

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Program #/Poster #: PSTR491.07/X32

Topic: I.04. Physiological Methods

Support: NIH Grant R01NS118289
Burroughs Wellcome Fund 1015761

Title: Fast Volumetric Miniaturized Two-Photon Microscopy in Freely-Moving Mice

Authors: *B. MATTISON, Z. ZHANG, S.-J. LIU, W. YANG;
Univ. of California Davis, Davis, CA

Abstract: Miniaturized two-photon microscopes are powerful optical tools for functional recording of neural activity at cellular resolution in freely-moving animals. Two-photon imaging traditionally requires mechanically raster scanning a small laser excitation spot over a large field-of-view (FOV) to generate each image frame. This point-by-point scanning approach limits the overall imaging frame rate. Miniaturized microscopes are further constrained by size and weight requirements as to not hinder the natural behavior of mice when attached to their skull. Here, we report a two-photon miniaturized microscope that can image neuronal activity with a high speed. Rather than illuminating the sample with a diffraction-limited spot, we shape the beam into an elliptical spot (5-10 μm in long axis) through two orthogonal cylindrical lenses and scan it across the FOV. This samples a large area of the neuronal cell body in a single measurement and effectively reduces the number of rows required for a single FOV, thus increasing the imaging frame rate for a given scanner speed. As the size of the elliptical beam spot is less than the cell body diameter (10-15 μm), our approach can maintain cellular resolution. The excitation point-spread-function was measured to be ~1.1 μm × ~7.3 μm full-width-half-maximum (FWHM) laterally and ~19 μm FWHM axially. We incorporated an electrically tunable lens to adjust the imaging depth dynamically. Using our miniaturized microscope, we performed fast volumetric calcium imaging in mouse visual cortex transfected with GCaMP calcium indicators. Compared to the point-by-point scanning approach, we achieved a ~5× increase in imaging speed through the elliptical beam excitation. We extracted neuronal activity through a non-negative matrix factorization algorithm. Our miniaturized two-photon microscope can record neural activity over a large 3D brain volume at a high speed in freely-moving mice and will be important to study large-scale neuronal circuits during natural mouse behaviors.

Disclosures: B. Mattison: None. **Z. Zhang:** None. **S. Liu:** None. **W. Yang:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR491.08/X33

Topic: I.04. Physiological Methods

Title: Simultaneous Multi-region Neuronal-Level Brain Imaging in Freely Behaving Mice

Authors: *T. MAHMOUDI[1], R. CHRISTO[2], Y. LEE[2], C. SANTOS[2], J. KANEM[1], A. PAPANICOLAOU[3];
[1]Bruker, Toronto, ON, Canada; [2]Bruker LTD., Toronto, ON, Canada; [3]Bruker LTD, Toronto, ON, Canada

Abstract: Understanding the circuit mechanisms underlying naturalistic behavior requires the simultaneous recording of neural activity in multiple brain regions correlated with behavior. We have previously reported on a multi-region miniscope, employing four highly flexible and lightweight imaging fiber bundles (IFBs), allowing imaging of up to four brain areas in freely

behaving subjects. Transgenic animals or viral expression are utilized to express Genetically Engineered Calcium Indicators (GECIs). Up to four GRIN Lens-Connectors (GLCs) can be surgically implanted into the brain regions of interest. These are designed with the capability of implantation at various angles and a focus-lock mechanism, facilitating imaging of hard-to-reach brain regions in birds, rodents, and juvenile animals. During an imaging-behavior session, the IFBs are connected to the implanted GLCs, transmitting illumination light from the LED source (470nm +/-12nm) to the implanted GLCs. Each GLC forms an image of neurons above its distal end from the brain, which is then transmitted to the camera via the same illumination IFB. This design keeps all optics away from the animal's head, allowing for lightweight implants (total <1.5g) with a small footprint, enabling four to fit on the head of a mouse. We now report how the multi-region miniscope is used to record neurons from multiple brain regions in one animal or 1-2 brain regions across multiple animals in an imaging session. We explain the data analysis workflow and assess metrics such as the average neuron count in the targeted brain regions, signal-to-noise ratio (SNR) and provide examples of neuronal traces to illustrate the quality of recordings. In addition, we detail the acceptance criteria of each calcium trace. We also assess the same matrix for longitudinal imaging, and how it evolves over time. The software offers live imaging and real-time analysis capability allowing simultaneous recording and analysis across multiple regions. We report imaging hundreds of neurons in the hippocampus (HPC), amygdala (BLA), and medial prefrontal cortex (mPFC) during open-field and swimming paradigms and compare the quality of traces using both manual ROI selection (our software) and automated ROI selection using PCA/ICA or NNMF (IDPS and IDEAS, Inscopix). Specifically, we look at the effect of the fall time of the calcium transient in calculation of SNR, compared to its shape. By observing calcium imaging data in different brain regions simultaneously, such as the HPC, BLA and mPFC, we can observe relationships between brain regions in order to better gain insight to neuronal activity across interconnected brain circuits.

Disclosures: T. Mahmoudi: A. Employment/Salary (full or part-time):; Bruker (Full-time). **R. Christo:** A. Employment/Salary (full or part-time):; Bruker (. **Y. Lee:** A. Employment/Salary (full or part-time):; Bruker (Full-time). **C. Santos:** A. Employment/Salary (full or part-time):; Bruker (Full-time). **J. Kanem:** A. Employment/Salary (full or part-time):; Bruker (Full-time). **A. Papanicolaou:** A. Employment/Salary (full or part-time):; Bruker (Full-time).

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR491.09/X34

Topic: I.04. Physiological Methods

Title: A miniature multiphoton microscope for simultaneously imaging superficial and deep cortical layers in freely moving mice

Authors: *A. KLIOUTCHNIKOV, D. J. WALLACE, J. N. KERR;
Max Planck Inst. for Neurobio. of Behavior, Bonn, Germany

Abstract: Miniature head-mounted three-photon microscopes enable imaging neuronal activity from populations of neurons located in the deepest cortical layers in freely-moving mice. While previous published miniature microscopes were mounted in a fixed position giving access to a single population of neurons, recent opto-mechanical Z-Drive designs and electrically tunable lenses have been introduced and allow adjustment of imaging planes over cortical layers. As cortical layers are functionally heterogeneous structures containing sub-populations of neurons that receive unique axonal inputs and in turn target distinct brain structures, one limitation of these approaches is the restriction of imaging neuronal activity simultaneously within one cortical layer or within a small volume. Here we present a new head-mounted microscope that combines both 2-photon-and 3-photon excitation in combination with a tunable electric lens allowing neuronal population imaging from 10 vertically separated imaging planes. This microscope weighs 2.5g and obtains frame rates of 30Hz while imaging ~100 neurons per imaging plane located across the cortical layers as the animal freely behaves. As this new multiplane head-mounted microscope allows neuronal activity to be simultaneously sampled from neuronal populations we are currently using this approach to investigate how sensory inputs are encoded across the visual cortex layers during visually based behavioral tasks in the freely moving animal.

Disclosures: A. Klioutchnikov: None. **D.J. Wallace:** None. **J.N. Kerr:** None.

Poster

PSTR491: Cutting-Edge Methods for Neuronal Monitoring and Control in Freely Moving Animals

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR491.10/X35

Topic: I.04. Physiological Methods

Support: DP2EY032737
Searle Scholars Program
Sloan Research Fellowship

Title: From Pixels to Navigation: Exploring Fruit Fly Vision with a Novel 330° VR Arena

Authors: D. NATESAN[1], K. KIM[2], ***S. JEE**[3], S. KIM[1,4];
[1]Molecular, Cellular, and Developmental Biol., [2]AlloSphere Res. Facility, [3]Dynamical Neurosci., UC Santa Barbara, Santa Barbara, CA; [4]Dynamical Neurosci., UC Santa Barbara, UC Santa Barbara, CA

Abstract: Vision is essential for animal navigation and fruit flies serve as an ideal model to explore how visual information influences navigation, given their diverse behavioral repertoire and accessible genetic tools for probing neural circuits. A controlled visual environment is

pivotal for studying how animals process visual information and perceive space. However, the compound eyes of fruit flies detect wavelengths spanning from 350nm (ultraviolet) to 600nm (amber), making it inadequate to use displays designed for humans. Furthermore, previous visual navigation experiments with fruit flies typically utilized LED arenas emitting only a single wavelength, which does not sufficiently mimic natural environments. To address this discrepancy, we developed a 330° full-color cylindrical virtual reality (VR) arena equipped with four 120 Hz projectors. This configuration covers the fly's 330° field of view and emits light corresponding to the absorption spectra of the fly's photoreceptors. This system projects images in three specific color channels: ultraviolet (385 nm), blue (460 nm), and amber (585 nm), deliberately omitting green (490 nm) and red (590 nm) to allow the arena to be used with dual-color two-photon calcium imaging. The system necessitates two critical calibration steps: geometric calibration and photometric calibration. Geometric calibration allows precise alignment and image continuity across projectors, correcting for the curvature of the cylindrical screen. Photometric calibration ensures uniform pixel illumination across all projectors and color channels, including blending over the regions where projector images overlap. We further developed a rendering pipeline that simulates virtual environments in software frameworks such as Unreal Engine 5 and renders it in real-time on the arena according to the navigational input from the fly, which allows exploration of various behavioral scenarios with minimal latency. This setup facilitates comprehensive behavioral analysis of fruit flies in controlled, realistic settings. Coupled with two-photon microscopy, our VR arena permits the detailed investigation of neural activities in brain regions involved in visually guided navigation under rigorously controlled experimental conditions.

Disclosures: D. Natesan: None. **K. Kim:** None. **S. Jee:** None. **S. Kim:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.01/Y1

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

Support: NSF GRFP
NINDS Brain Initiative RF1 MH114252
NINDS UG3 NS114438
NINDS HEAL Initiative UG3 NS115637
Stanford Wu Tsai Neurosciences Institute
NIH/NIMH

Title: Brain regional specificity of ketamine action at low doses revealed by ultrasonic drug uncaging using acoustomechanically activatable liposomes

Authors: *B. J. YU[1], S. N. EWBANK[1], K. SINHA ROY[1], M. M. AZADIAN[1], M. PUROHIT[1], Y. XIANG[1], J. B. WANG[2], A. TAOUBE[1], E. MARKARIAN[1], N. MACEDO[1], D. GOMEZ

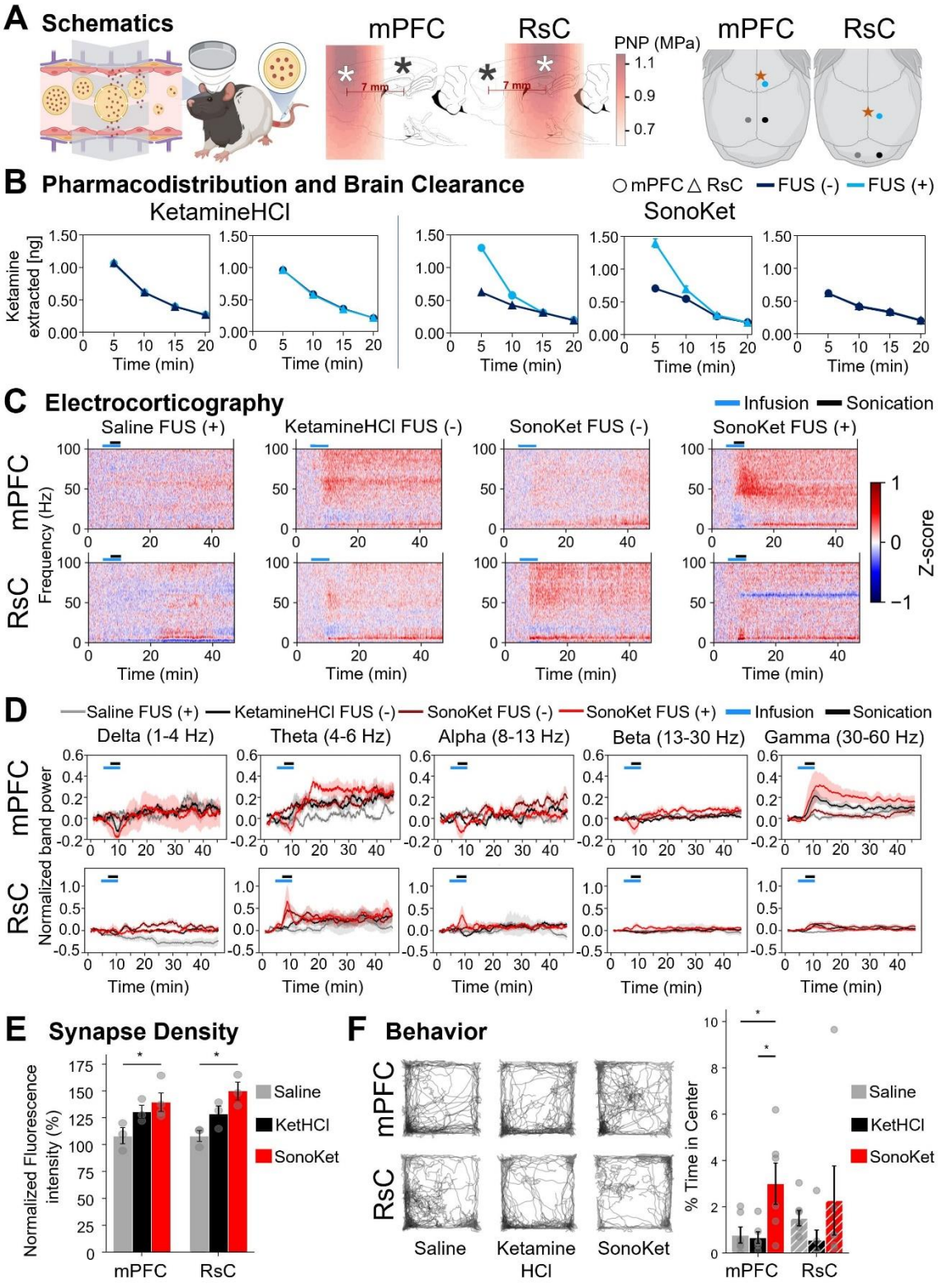
LOPEZ[3], R. AIRAN[1];
[1]Stanford Univ., Palo Alto, CA; [2]Anesthesia and Critical Care, John Hopkins Hosp., Baltimore, MD; [3]Vanderbilt Univ., Nashville, TN

Abstract: The varied therapeutic effects of ketamine are attributed to action at spatially distinct brain regions. For example, its affective efficacy has been attributed to the medial prefrontal cortex (mPFC) and its dissociative effects to the retrosplenial cortex (RsC). To causally establish these relationships and to potentially leverage them clinically, we developed a translation-ready ultrasound-sensitive liposomal formulation of ketamine (SonoKet), which selectively uncages ketamine with focused ultrasound (FUS; A, left).

We determined the brain ketamine levels (A, middle; *: sampled sites) following free ketamine (KetamineHCl) or SonoKet administration (0.75 mg/kg IV/5 min), with FUS applied to either the mPFC or RsC in adult male Long Evans rats. FUS did not change the pharmacodistribution or clearance of KetamineHCl, with equivalent uptake in both brain regions (B, left; N=3-5/group). In contrast, with SonoKet, FUS (250 kHz; 1.1 MPa peak negative pressure, PNP; 50 ms/5 Hz PRF/2.5 min) yielded higher brain ketamine levels vs sham (B, right; N=3-5/group), indicating an uncaging spatial resolution of <7 mm.

Electrocorticography (A, right) during awake restraint stress showed no specific change with FUS alone. Gamma and theta power increases were seen with mPFC SonoKet uncaging, curiously to higher levels than dose matched KetamineHCl infusion (C, D). In contrast, with RsC uncaging spikes of theta, alpha, and beta power were observed, in a pattern distinct from mPFC uncaging and dose matched KetamineHCl infusion (C, D).

Ketamine uncaging in each brain region yielded higher PSD95 staining as a marker of synaptogenesis (E, *: $p<0.05$, N=4/group). Pivotally, open-field tests showed that with mPFC ketamine uncaging rats showed increased center time, indicating a lower stress response to acute awake restraint with no significant change with KetamineHCl infusion or RsC uncaging (F, *: $p<0.05$, N=8/group). These results using a translation-ready system for noninvasive targeted drug delivery confirm the unique regionally specific physiologic and behavioral effects of ketamine.



Disclosures: B.J. Yu: None. **S.N. Ewbank:** None. **K. Sinha Roy:** None. **M.M. Azadian:** None. **M. Purohit:** None. **Y. Xiang:** None. **J.B. Wang:** None. **A. Taoube:** None. **E. Markarian:** None. **N. Macedo:** None. **D. Gomez Lopez:** None. **R. Airan:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.02/Y2

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

Support: Lundbeck Foundation
Novo Nordisk Foundation
Academy of Finland (grant no 350371)
Finnish Medical Foundation
Paulo Foundation
Sigrid Jusélius Foundation
Emil Aaltonen Foundation
University of Helsinki Research Funds
The Acta Anaesthesiologica Scandinavica Foundation
University doctoral school, University of Helsinki

Title: Head over heels: Systemic hypertonic saline draws lumbar intrathecal administered drugs to the intracranial space

Authors: *N. PERSSON[1,2,3], J. N. MÄKELÄ[1], J. E. ANTTILA[1,3], M. ROSENHOLM[6,3], T. J. LOHELA[7,1,3], M. PELTONIEMI[3,1], M. SARPARANTA[4], M. NEDERGAARD[9,6], T. P. RANTAMAKI[3,5], T. O. LILIUS[1,3,2,8];
[1]Individualized Drug Therapy Res. Program, Fac. of medicine, [2]Dept. of Pharmacology, Fac. of medicine, [3]Div. of Pharmacol. and pharmacotherapy, Fac. of Pharm., [4]Dept. of Chemistry, Fac. of Sci., [5]SleepWell Res. Program, Fac. of Med., Univ. of Helsinki, Helsinki, Finland; [6]Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark; [7]Anaesthesiology, Intensive Care and Pain Med., [8]Dept. of Emergency Med. and Services, HUS Helsinki Univ. Hosp. and Univ. of Helsinki, Helsinki, Finland; [9]Ctr. for Translational Neuromedicine, Univ. of Rochester, Rochester, NY

Abstract: Background and aim: More efficient approaches to treat neurological diseases are needed to tackle their heavy and increasing burden on healthcare systems. To largely bypass the blood-brain barrier and limit systemic side effects, a drug can be administered directly to the cerebrospinal fluid (CSF). Preclinical studies have demonstrated enhanced brain delivery of a drug or tracer administered into the cisterna magna by systemic co-administration of hypertonic saline (HTS) or hyperosmolar mannitol compared to isotonic saline (ITS). Lumbar intrathecal administration is a routine procedure in clinical practice while the use of cisterna magna infusion has been mostly limited to preclinical studies due to its invasiveness. In the present study, we investigated whether systemically co-administered HTS enhances intracranial delivery of intrathecal lumbar infused tracer as a novel method to improve the efficacy of brain-targeted drugs.
Methods: Female rats under ketamine-dexmedetomidine (KDEX) anesthesia received a lumbar

catheter at the T13-L1 level. Radiolabeled ^{99m}Tc-human serum albumin nano-colloid (^{99m}Tc-nanoHSA, size 66.5 kDa) was infused (25 μL, 2 μL/min) intrathecally followed by slow injection of intraperitoneal HTS (1 M, 20 ml/kg) or ITS (0.154 M, 20 ml/kg). Full-body distribution of ^{99m}Tc-nanoHSA in dynamic in vivo SPECT was assessed for 2 hours. In another set of experiments performed to investigate long-term effects of HTS, rats were allowed to recover from the catheterization and anesthetized with isoflurane (ISO) to acquire SPECT images of whole-body distribution of intrathecally infused ^{99m}Tc-nanoHSA at 0, 3, 6, and 24 hours post-infusion. In this set of animals HTS or ITS was injected directly before tracer administration.
Results: HTS increased intracranial tracer availability significantly (2 % of injected dose at 2 hours after administration) in KDEX anesthetized rats while no tracer could be detected in the intracranial space up to 2 hours after infusion in the ITS group. Further, 96% of tracer was retained in the CNS at 2 hours after the infusion compared to barely 80% in the ITS group. In the longer experiments the HTS group exhibited a nearly doubled maximum tracer activity in the intracranial space compared to ITS (2.1 vs. 1.3 % of injected dose, at 3 hours) under ISO anesthesia, with lasting effect (1.9 % vs. 1 %, at 24 hours).
Conclusions: HTS enhanced delivery of lumbar intrathecal tracers to the intracranial space, with the effect lasting for the 24 hours of our study. The HTS-enhanced brain delivery of lumbar intrathecal administered drugs should be taken to clinical trials.

Disclosures: N. Persson: None. **J.N. Mäkelä:** None. **J.E. Anttila:** None. **M. Rosenholm:** None. **T.J. Lohela:** None. **M. Peltoniemi:** None. **M. Sarparanta:** None. **M. Nedergaard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent Application for GLYMPHATIC DELIVERY BY MANIPULATING PLASMA OSMOLARITY Patent Application (Application #20220280423). **T.P. Rantamaki:** None. **T.O. Lilius:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent Application for GLYMPHATIC DELIVERY BY MANIPULATING PLASMA OSMOLARITY Patent Application (Application #20220280423).

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.03/Y3

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

Support: VA RR&D RX002305

Title: Assessing blood-nerve barrier permeability to nanoparticles over the course of experimental autoimmune neuritis

Authors: *C. KAUR[1], M. H. CABE[2], Z. ADELSTEIN[3], R. SIRIANNI[4], K. A. LANGERT[5]; [1]Loyola Univ. Chicago, brookfield, IL; [2]Mol. Pharmacol. and Neurosci., Loyola Univ. Chicago,

Maywood, IL; [3]Loyola Univ. Chicago, Stritch Sch. of Med., maywood, IL; [4]UMass Chan Med. Sch., Worcester, MA; [5]Loyola Univ. Chicago, Oak Park, IL

Abstract: The acute inflammatory demyelinating polyneuropathy (AIDP) subtype of Guillain-Barré syndrome (GBS) is a debilitating autoimmune peripheral neuropathy. Treatment options are limited to nonspecific immunomodulation and are often ineffective. Systemic or local delivery of several candidate therapeutics have been demonstrated to attenuate the severity of experimental autoimmune neuritis (EAN), an established rat model of AIDP. However, the advancement of these findings has been limited due to high doses or impractical routes of administration that are not clinically translatable. While the blood-nerve barrier (BNB) normally restricts access of circulating molecules to the endoneurium, during the acute inflammation associated with some peripheral neuropathies, including AIDP, the BNB exhibits increased vascular permeability and enables immune cell infiltration. These pathological changes contribute to disease, but they may also offer a unique opportunity to access the otherwise restricted peripheral nerve microenvironment for therapeutic delivery. In other fields, it is established that circulating particles with favorable size and morphology will passively accumulate in sites with fenestrated vasculature through an enhanced permeation and retention process. In this work, we tested the hypothesis that nanoparticles (NPs) with surfaces modified for prolonged circulation will accumulate in affected nerves in rats with EAN through a similar process. We assessed BNB permeability to intravenously administered small molecules (Evan's Blue Dye) and spectrally defined NPs (58 and 134 nm polystyrene) over the length of the nerve and the course of EAN. NPs were obtained as commercially available, carboxylated Fluospheres to which we covalently attached poly(ethylene) glycol (PEG) amine using carbodiimide coupling. We also quantified immune cells present in nerve cross-sections and compared our findings to naïve rats to determine the correlation between immune cell infiltration, BNB permeability, and NP accumulation. Results demonstrate increased BNB permeability to small molecules at disease onset and permeability to NPs up to 134 nm in size during the intermediate to peak stages of the disease. NP permeability coincides with CD68+ macrophage infiltration.

Disclosures: C. Kaur: None. **M.H. Cabe:** None. **Z. Adelstein:** None. **R. Sirianni:** None. **K.A. Langert:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.04/Y4

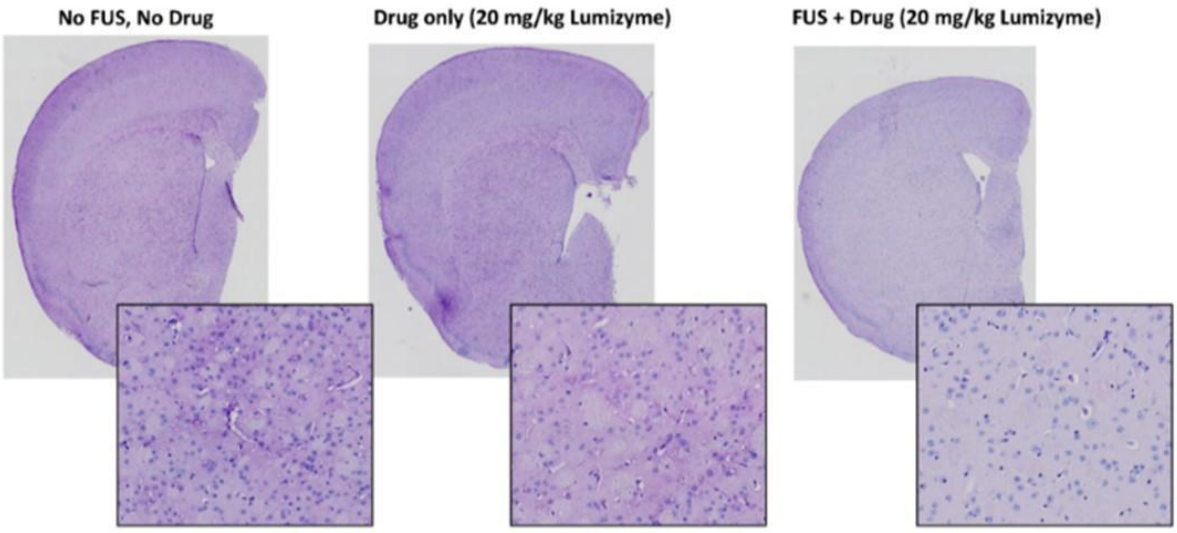
Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Sanofi

Title: Enabling CNS Delivery of rhGAA in GAA KO Mice using Focused Ultrasound

Authors: *P. NOWLIN[1], Y. ZHANG[1], A. CHISHOLM[1], S. YOUNG[2], D. BALI[2], N. TODD[1]; [1]Brigham and Women's Hosp., Boston, MA; [2]Duke Univ., Durham, NC

Abstract: The objective of this study is to achieve the delivery of enzyme replacement therapies (ERTs) with recombinant human alglucosidase alfa (rhGAA) to the central nervous system (CNS). The clinically used ERT Lumizyme (rhGAA) has been very successful in mitigating pathology in peripheral organs of Pompe disease (PD) patients, but the therapy does not cross the blood brain barrier (BBB). Over time PD patients develop cognitive deficits, neurodegeneration, and fatigue due to toxic lysosomal glycogen accumulation in the CNS. Focused ultrasound (FUS) BBB opening is a promising treatment for achieving delivery of non-penetrant therapeutics to specific brain regions in a focal zone of only a few millimeters. We investigated glycogen accumulation in 5-month-old GAA knockout (KO) mice following ERT administration and FUS-BBB opening. 24 mice were divided into four groups (n=6 per group); each underwent 4 biweekly treatments based on group description. FUS groups received systemic injection of 20mg/kg Lumizyme following BBB opening or BBB opening without ERT administration. NO FUS groups either received only Lumizyme or remained untreated. BBB opening was targeted to the striatum bilaterally in each mouse. Diphenhydramine (10mg/kg) was administered 10 minutes prior to ERT administration to avoid anaphylactic response. Microbubbles (20µL/kg) were administered via tail vein catheter and sonications were applied at 10ms bursts and 1Hz frequency over 120 seconds at 0.32 MPa. BBB disruption was confirmed using contrast MRI following opening. Mice were sacrificed and brains harvested 24 hours after the final treatment. Each brain was bisected, one hemisphere flash frozen for protein analysis the other was fixed, stored in PBS, and processed for glycogen accumulation analysis using the Periodic Acid Schiff stain (PAS). Each stained hemisphere was analyzed. We observed a significant reduction in glycogen in the FUS+ERT groups compared to the ERT only group ($p<0.001$). Figure 1 shows representative PAS-stained samples from each group. Protein analysis for GAA enzyme and Hex4 levels is ongoing.



Disclosures: P. Nowlin: 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.; Sanofi. **Y. Zhang:** None. **A. Chisholm:** None. **S. Young:** None. **D. Bali:** None. **N. Todd:** 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.; Sanofi.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.05/Y5

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

Title: Systemic delivery of oligonucleotide transport vehicle (OTV) for targeted ASO therapy in neurological disorders

Authors: *V. WARKINS[1], S. BARKER[2], M. THAYER[2], M. SIMON[3], J. W. LEWCOCK[2]; [1]Denali Therapeut., San Francisco, CA; [3]Translational Sci., [2]Denali Therapeut., South San Francisco, CA

Abstract: Antisense oligonucleotides (ASOs) hold immense therapeutic potential for neurological disorders by modulating gene expression at the RNA level. However, their efficacy is hindered by the inability to efficiently cross the blood-brain barrier (BBB) for central nervous system (CNS) delivery. Utilizing a human transferrin receptor (TfR)-binding moiety, we have developed a novel vehicle, termed oligonucleotide transport vehicle (OTV), aimed at facilitating the delivery of antisense oligonucleotides (ASO) across the blood-brain barrier (BBB) without the need for direct delivery into the CNS. Compared to conventional delivery methods such as administering a high-affinity TfR antibody or directly delivering ASOs to the cerebrospinal fluid (CSF), systemic OTV delivery ensures a more uniform distribution of ASOs and target knockdown. Systemically injecting OTV has resulted in significant, cumulative, and sustained reduction of the ASO target across various regions of the CNS and all major cell types. Together, our data support systemically delivered OTV as a potential therapeutic platform for neurological disorders.

Disclosures: V. Warkins: A. Employment/Salary (full or part-time):; Denali Therapeutics. **S. Barker:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **M. Thayer:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **M. Simon:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **J.W. Lewcock:** A. Employment/Salary (full or part-time):; Denali Therapeutics.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.06/Y6

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

Support: National Defense Science and Engineering Graduate Fellowship
R01DA51100
R01AI145206

Title: Eab sensors for a comprehensive understanding of chemotherapeutic distribution across the blood brain barrier

Authors: *N. A. EMMONS;
Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: EAB sensors enable seconds-resolved quantification of chemotherapeutic distribution across the blood brain barrier
Figure 1: The in brain EAB platform consists of a 75 μm-diameter, 3-mm-long gold electrode that extends from a 22-gague stainless steel counter/pseudo-reference electrode. (B) These probes are inserted into brain regions of interest following stereotaxic surgery.
The treatment of in-brain cancers is significantly limited by the failure of chemotherapeutics to permeate the BBB (blood-brain barrier). Doxorubicin has been demonstrated to effectively inhibit the proliferation of glioma cells in vitro and is highly toxic to glioblastoma cell lines in vivo, yet when intravenously administered, doxorubicin has poor permeation across the BBB. Researchers have developed a host of new technologies and drug delivery methods aimed at enhancing the permeation of chemotherapeutics, specifically doxorubicin, across the BBB, to overcome this obstacle. Despite these breakthroughs, existing methods for in-brain molecular monitoring lack the temporal resolution to understand how these manipulations dynamically alter the kinetics of drug distribution into the brain. Toward this aim, this work utilizes electrochemical aptamer-based (EAB) sensors to better elucidate chemotherapeutic transport across the blood brain barrier. Consisting of a 75 μm, 3-mm long gold wire electrode, EAB sensors can be implanted into the brain following stereotaxic surgery and can be used to analyze in-brain drug concentrations with high temporal resolution, a vast improvement to traditional sampling techniques such as microdialysis (Fig. 1). Utilizing EAB sensors, I first demonstrate that doxorubicin does not permeate the BBB in detectable amounts (Fig 2.). I use this platform to explore how different formulations of doxorubicin, including pegylated liposomal doxorubicin and glutathione doxorubicin, alter the transport kinetics and facilitate transport across the blood-brain barrier. This is the first work of its kind to capture and compare, with seconds-resolved temporal resolution, how different drug delivery systems can alter in-brain drug levels. **Figure 2. Doxorubicin does not permeate the BBB in detectable amounts. (A) Surgical manipulations performed for the placement of EAB sensors do not disrupt the BBB, evidenced by the lack of permeation of doxorubicin into the brain following a large dose of drug. (B) The doxorubicin aptamer is sensitive to detection of small amounts of drug, as evidenced by the titration curve in 37° CSF (Kd = 4.4). If doxorubicin was permeating the BBB, our sensor would be sensitive enough to detect increases in doxorubicin in the brain**

Disclosures: N.A. Emmons: None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.07/Y7

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

Support: NIH R44CA239830

Title: A novel image guided focused ultrasound platform for therapeutic delivery across the blood-brain barrier in mice

Authors: P. DURHAM[1], V. PAPADOPOULOU[2], *Z. H. HOUSTON[3], **K. C. KLOEPPING**[4], P. DAYTON[5], T. J. CZERNUSZEWICZ[6], R. GESSNER[7];
[1]The Joint Dept. of Biomed. Engin., The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Radiology & Biomed. Engin., The Univ. of North Carolina at Chapel Hill and North Carolina State Univ., Chapel Hill, NC; [3]Revvity, Inc., Hopkinton, MA; [4]Revvity, Inc., Waltham, MA; [5]Biomed. Engin., The Univ. of North Carolina at Chapel Hill and North Carolina State Univ., Chapel Hill, NC; [6]Revvity, Inc., Durham, NC; [7]Revvity, Durham, NC

Abstract: Blood-brain barrier (BBB) penetration is a significant challenge for the treatment of many neurological disorders and diseases of the brain. Focused ultrasound (FUS) therapy has shown efficacy against brain disease targets due to its ability to transiently disrupt the BBB. FUS is applied external to the body, with or without injectable microbubble contrast agents, and exerts thermal and mechanical bioeffects by targeting ultrasound energy deposition in a specific area making it an ideal direct treatment or adjuvant treatment option. To limit off-target effects, an important component of FUS is the use of image guidance to delineate the treatment area and ensure that only a specific spatial region will be targeted. Herein we present a modification to a commercially available robotic preclinical ultrasound system that allows for whole-body mouse imaging and image guidance of FUS delivery to user-defined targets. We evaluate its inter-user targeting accuracy in an acoustically responsive phantom material and demonstrate its ability to open the BBB in a mouse model, using ex vivo fluorescence imaging (FLI) for validation. By leveraging ultrasound guidance, this system provides a theranostic platform for precise FUS delivery with anatomical and functional imaging, in a user interface that facilitates custom treatment definitions and reduces ultrasound operator variability. This unique combination is a significant first step in providing better tools for preclinical studies and lowering the barrier of entry for researchers to investigate novel therapeutic targets for neurological diseases.

Disclosures: P. Durham: None. **V. Papadopoulou:** None. **Z.H. Houston:** A. Employment/Salary (full or part-time):; Revvity, Inc. **K.C. Kloepping:** A. Employment/Salary (full or part-time):; Employee at Revvity, Inc. **P. Dayton:** 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 grants through National Institutes of Health. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); C equipment loaned from Revvity, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Stock/Stock Options in Triangle Biotechnology and SonoVascular. Intellectual property holder and royalties from Revvity, Triangle Biotechnology, SonoVascular.. F. Consulting Fees (e.g., advisory boards); Advisory Board member for Triangle Biotechnology and SonoVascular. **T.J. Czernuszewicz:** A. Employment/Salary (full or part-time):; Employee at Revvity, Inc. **R. Gessner:** A. Employment/Salary (full or part-time):; Employee at Revvity, Inc..

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.08/Y8

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

Title: Advancements in Epidural and Intrathecal Delivery Techniques for Novel Genetic Therapeutics in Preclinical Rat Models.

Authors: *K. KELLY[1], C. PRIDDY[1], S. LING[1], E. P. FURBER[2], A. LEE-GOSSELIN[1], E. O'NEIL[3], J. LI[1], A. WROBLESKI[1], B. LI[3], J. HUANG[4], F. BASSIL[1], B. L. ADAMS[5]; [2]Prevail Therapeut., [3]Neurosci., [1]Eli Lilly and Co., Indianapolis, IN; [4]Eli Lilly and Co., Boston, MA; [5]Global Pain Res. and Develop., Lilly Res. Labs, Indianapolis, IN

Abstract: The development of genetic medicines holds tremendous promise for revolutionizing medical treatment across a spectrum of diseases. However, before these innovative therapies can progress to clinical trials and eventual patient use, rigorous preclinical testing is essential. Rodent models serve as indispensable tools in this process, offering valuable insights into the safety, efficacy, and mechanisms of action of potential treatments. Here, we explored and developed methods for the accurate delivery of these therapeutics to challenging tissues in the rat, specifically the spinal cord and dorsal root ganglions (DRGs). Percutaneous intrathecal administration was performed in anesthetized rats by locating spinal process markers that targeted the L5/L6 space. Epidural administration was a surgical cut-down method where a Tuohy guide needle was inserted into L5/6 and a small cannula fed through the epidural space away from the needle insertion site. Accuracy of injection site was confirmed with dye injection, where intrathecal administration resulted in complete staining of the spinal cord cross section and epidural administration had limited staining outside the spinal cord and local DRGs. The ability of the AAV9-eGFP to transfect cells after intrathecal or epidural administration was assessed in the spinal cord, DRGs and brain by secondary antibody staining. The overall signal was lower than expected, but GFP expression was observed in brain regions, spinal cord and DRGs with both routes. Taken together, our data suggests that epidural administration of rAAV therapeutics may offer access to both spinal and DRG targets, potentially with more local restriction than intrathecal dosing. Importantly, epidural administration is already widely performed in clinical practice, representing an attractive delivery route for spinal and DRG genetic medicine targets.

Disclosures: K. Kelly: A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **C. Priddy:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **S. Ling:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **E.P. Furber:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **A. Lee-Gosselin:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **E. O'Neil:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **J. Li:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **A. Wrobleski:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **B. Li:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **J. Huang:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **F. Bassil:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co. **B.L. Adams:** A. Employment/Salary (full or part-time):; Lilly Research Labs, Eli Lilly & Co..

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.09/Y9

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

Title: Assessment and Utilization of EnClear Technology for Controlled Cerebrospinal Fluid Flow within the Non-Human Primate at a Preclinical Contract Research Laboratory with Implications for IND-Enabling Studies.

Authors: S. WOODS[1], J. J. DEVRIES[1], J. OGLE[1], J. E. GESAMAN[1], D. LINIHAN[1], S. WILSON[1], M. A. GLICKSMAN[2], A. DEPASQUA[2], K. KALISH[2], ***B. GUNTER**[1]; [1]Charles River Labs., Mattawan, MI; [2]EnClear Therapeut., Cambridge, MA

Abstract: Delivery of therapeutics with central nervous system (CNS) indications that cannot readily cross the blood brain barrier require a surgical approach. Distribution within the CNS is highly dependent on targeted delivery to the region of interest or delivery within the cerebrospinal fluid (CSF). Routes of administration to the CSF in the intrathecal space include intracerebroventricular, intracisternal magna, or within the lumbar cistern. Each route has its own unique benefits and challenges and have been shown to affect the distribution of the therapeutic, in particular gene therapies. As such, a technique that can influence and control CSF flow within the system can possibly improve distribution to the targeted sites of interest within the CNS. At our GLP- compliant contract research laboratory, we initiated pilot studies using EnClear's technology and assessed several flow directions and speeds within an anesthetized non-human primate. Briefly, the lateral ventricles of the brain were targeted via MRI and stereotactic surgery. A spinal needle was then lowered into the ventricle and administration of Omnipaque contrast through the spinal needle confirmed placement in the lateral ventricle. Furthermore, a catheter was placed in the intrathecal space of the lumbar cistern and the location was confirmed using contrast. The intracerebroventricular and intrathecal access points were then attached to EnClear's system, and CSF recirculation was performed. The CSF flow, pressure, and vital signs

were continuously monitored with the EnClear sensor array. Multiple images were captured using fluoroscopy at different stages of recirculation. Once the procedure was complete, the animals' vitals were monitored. The results confirm the EnClear system is a clinically relevant method for controlling CSF flow within the non-human primate with high level of accuracy. Furthermore, refinements executed during these pilot sessions improved functionality of the workflow and will be critical for improving CNS drug delivery and distribution in patients. Importantly, this early work was pivotal in providing critical feedback for future non-GLP and GLP studies investigating efficacy and safety of Sponsor test articles.

Disclosures: S. Woods: None. **J.J. DeVries:** None. **J. Ogle:** None. **J.E. Gesaman:** None. **D. Linihan:** None. **S. Wilson:** None. **M.A. Glicksman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EnClear Therapeutics. **A. DePasqua:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enclear Therapeutics. **K. Kalish:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Enclear Therapeutics. **B. Gunter:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.10/Y10

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

Support: R01 DA040630
NSF GRFP 1937963

Title: Trping on drugs: a hot new candidate for intracellular drug delivery in the brain

Authors: *J. ZEPEDA[1], P. C. ADAPA[1], B. A. GRUETER[2];
[1]Vanderbilt Univ., Nashville, TN; [2]Anesthesiol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: The nucleus accumbens (NAc) is a limbic-motor interface that guides motivated behaviors and is robustly engaged by psychostimulants such as cocaine. Previous studies have shown functional activity of the transient receptor potential vanilloid 1 receptor (TRPV1) within the NAc. An agonist induced dilation of TRPV1 is permeant to positively charged small molecules, including the membrane-impermeable sodium channel blocker QX-314. Additionally, it has been shown that mice which lack TRPV1 express an increased locomotor response to cocaine. We hypothesized that the QX-314 could enter cells through TRPV1's large pore and block action potentials in TRPV1-expressing cells to decrease cocaine hyperlocomotion. We used anatomically precise behavioral pharmacology in mice to assess the effects of capsaicin and QX-314 microinjections into the NAc on cocaine-induced hyperlocomotion. We report that microinfusing QX-314 and capsaicin into the NAc before a cocaine injection decreases the

distance traveled by mice with comparison to a vehicle control group. However, when we infused capsaicin, QX-314 and the TRPV1 antagonist AMG 9810 together, cocaine-induced hyperlocomotion was robustly increased, reversing the effects of QX-314 and capsaicin. To validate entry of QX-314 into MSNs in the NAc, we performed whole whole-cell voltage clamp electrophysiology to assess the generation of action potentials by capsaicin and QX-314. We observe that action potential generation is significantly reduced when we bath apply capsaicin and QX-314, and that the reduction in action potential probability can be blocked by AMG 9810. Our results show that TRPV1 allows for the permeation of QX-314 into cells *in vivo* and provides an avenue for cell-specific drug delivery in the brain. Importantly, these studies advance the possibility for cell-specific targeting with pharmacological tools in the brain.

Disclosures: J. Zepeda: None. **P.C. Adapa:** None. **B.A. Grueter:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.11/Y11

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

Title: Aav(bbb)s: novel aav variants with 500-fold higher bbb crossing efficiency in nhp

Authors: *B. WANG[1], M. RODRIGUEZ[2], Y. LIU[1], C. XU[1], Z. SHI[1], W. SMITH[2], M. JIANG[2], Q. WANG[1], D. YU[1];
[1]AAVnerGene Inc., Rockville, MD; [2]John Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: AAV(BBB)s: Novel AAV Variants with 500-fold HigherBBB Crossing Efficiency in NHPBing Wang [1], Matt Rodriguez[2], Yu Liu[1], Cheng Xu[1], Yuling Dai[1], Jinjin Cai[1], Yuyan Wang[1], Lemin Wang[1],May Rose Chen[1], Zhen Shi[1], Danhui Lu[1], Wanli Smith[2], Mali Jiang[2], Qizhao Wang[1]* and Daozhan Yu[1]*[1]AAVnerGene Inc, 9620 Medical Center Dr, Suite 100, Rockville, MD, USA, 20850[2]Division of Neurobiology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins UniversitySchool of Medicine, Baltimore, Maryland, USA*Corresponding to qizhao.wang@aavnergene.com; Daozhan.yu@aavnergene.com; mjiang5@jhmi.eduGene therapy targeting CNS diseases faces significant challenges primarily due to the blood-brain barrier (BBB), which restricts the entry of therapeutic delivery vehicles. Adeno-associated virus serotype 9 (AAV9) has become a focal point in CNS gene therapy due to itsability to cross the BBB in mouse models. AAV9 serves as a foundational template fordeveloping new AAV vectors with enhanced BBB penetration capabilities, such as AAV-Php.eB. However, AAV capsids that were modified for BBB crossing in mice have shownlimited success in non-human primates (NHPs). To explore potential mechanisms, wesystematically assessed commonly used AAV serotypes (AAV1-AAV13), known BBB-crossing variants, and other popular engineered capsids using our ATHENA I platform, whichincorporates DNA barcode technology. Our findings confirmed that AAV9 remains thesuperior template for BBB-crossing selection in B6C3 mice. Variants like AAV-9P31, AAV-

F,AAV-Php.C2, and AAV-Php.eB were the most effective in most brain tissues. Nonetheless, inNHP models, AAV9 variants did not exhibit enhanced BBB crossing capabilities and showedvery low DNA levels compared to mouse models. Using our ATHENA I platform, we identifieda novel AAV capsid, termed AAV(BBB), which displayed a remarkable approximately 140-fold increase in DNA accumulation in the NHP brain relative to AAV9, and double the RNAlevels. To further enhance RNA expression, we evolved this capsid using our ATHENA III DNAshuffling platform. The resulting AAV(BBB) variants demonstrated up to a 500-fold increasein DNA and/or a 10-fold increase in RNA levels across the BBB in NHPs. Moreover, someAAV(BBB) variants showed a specific affinity for the NHP brain, with significantly reducedDNA accumulation and RNA expression in other organs. This breakthrough underscores the
potential of AAV(BBB) variants as promising candidates for CNS gene therapy, setting thestage for further research and development in this promising area.

Disclosures: B. Wang: None. **M. Rodriguez:** None. **Y. Liu:** None. **C. Xu:** None. **Z. Shi:** None. **W. Smith:** None. **M. Jiang:** None. **Q. Wang:** None. **D. Yu:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.12/Y12

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

Support: NIH Grant P20GM103395
NIH Grant R03MH135358
Office of Naval Research Grant N00014-18-1-2725

Title: Development of a novel alpha7-nAChR-selective dual drug delivery system for targeted siRNA transport.

Authors: *L. WEBER[1], B. OBRIEN[2], M. M. WELTZIN[2];
[1]Univ. of Alaska, Fairbanks, AK; [2]Univ. of Alaska Fairbanks, Fairbanks, AK

Abstract: Delivery of siRNA or nanoparticles into the central nervous system (CNS) by peripheral injection is possible by complexing with cell-penetrating peptides (CPP). However, current CPPs lack selectivity for specific cellular macromolecules, limiting their applicability. CPPs derived from the rabies virus glycoprotein (RVG) can access the CNS through binding to plasma membrane targets, including, but not exclusively, nicotinic acetylcholine receptors (nAChRs). RVG-derived CPPs make use of receptor-mediated mechanisms to enter the mouse CNS to deliver therapeutic cargo. Previous RVG-derived peptides lack specificity for a single molecular target, impeding their delivery of therapeutic cargo to specific cells or brain regions associated with distinct neurological diseases. For example, an overexpression of the α7-nAChR is involved in major depressive disorder (MDD). Therefore, an α7-nAChR-selective peptide that

has dual capabilities to antagonize receptor function and transport therapeutic cargo into α7-nAChR expressing neurons represents a potential novel treatment strategy. We hypothesized we could develop such a dual drug delivery system by combining regions of the RVG with segments of a protein known to selectively interact with α7-nAChRs. Previously we have shown that our chimeric peptide is an α7-nAChR selective competitive antagonist. We now aim to determine the chimeric peptide internalization and cargo-carrying properties using neuronal-like mammalian cells. To assess α7-nAChR selectivity, N2a cells were cultured and transfected with either α7-nAChR and NACHO DNA, or α7-nAChR siRNA to knockdown endogenous α7-nAChRs. The control RVG-CPP and our chimeric peptide were fluorescently tagged with FITC to track peptide location during live cell confocal microscopy. Fluorescence was quantified using ImageJ and revealed that our chimeric peptide enters mammalian cells by an α7-nAChR-mediated mechanism. Further, it can transport small molecules into neuronal-like cells, demonstrating that we have generated a novel CPP. To test the siRNA delivery potential of our innovative α7-nAChR selective CPP, we complexed fluorescein-labeled siRNA to our untagged chimeric CPP. siRNA complexed to our α7-selective chimeric CPP was observed to be delivered into cells more efficiently than by the RVG-CPP or a conventional transfection reagent. Our novel α7-nAChR subtype-selective CPP may be useful in research applications requiring cargo delivery. Translationally, our α7-nAChR selective CPP holds potential to be a dual drug delivery system to transport cargo into the brain for the treatment of neurological diseases, including MDD.

Disclosures: L. Weber: None. **B. OBrien:** None. **M.M. Weltzin:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.13/Y13

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

Title: Development of Surgical Procedures for Administration of Therapeutics to the Peripheral Nervous System via Ultrasound Guided Perineural Injection in Dogs and Göttingen Minipigs

Authors: *D. LINIHAN, R. DAVIS, J. GESAMAN, A. SCHULTE, S. WILSON, C. WILKEY-DERIDDER, B. GUNTER;
Surgery and Efficacy, Charles River Labs., Mattawan, MI

Abstract: Delivery of therapeutics with peripheral nervous system (PNS) indications such as neuralgia, nerve injury, neuropathy, or joint pain associated with osteoarthritis, may require a minimally invasive surgical approach for targeted administration. Often in preclinical drug assessment, the selection of the animal model utilized is based on comparable anatomy to humans. Therefore, the availability of multiple large animal models, each with subtle anatomical differences that may be relevant to the intended PNS indication, is a necessary option when selecting a preclinical animal species. Recently, Charles River-Mattawan developed techniques for administering therapeutics within the PNS, specifically perineural administration to the

sensory nerves (peroneal, saphenous, tibial) of the stifle joint in beagle dogs and the ulnar nerve in Göttingen Minipigs using ultrasound guidance to visualize and appropriately target each location. Pilot work was initiated in both dogs and minipigs to assess suitability of each species as a model for perineural adminstration. Assessment of the ultrasound transducer placement in correlation to the target nerve area, ideal mA settings on the nerve stimulator (Stimpod) to establish nerve location without penetration, as well as the maximum achievable dose volume were then evaluated. Both contrast dye and Fast Green were injected to confirm location to the target area and tissues were collected to confirm accurate targeting of the intended location. Successful administration of up to 3 mL in dogs via bilateral injection to peroneal, saphenous, and tibial nerves and 2 mL in minipig via ulnar nerve injection was achieved and animals were recovered out to 7 days post injection with minimal to no clinical signs. The success of this pilot work indicates that both species are suitable models for perineural administration. Future studies utilizing these procedures will assess distribution in the target nerves, systemic distribution, as well as future work targeting motor nerves.

Disclosures: D. Linihan: None. **R. Davis:** None. **J. gesaman:** None. **A. Schulte:** None. **S. Wilson:** None. **C. Wilkey-DeRidder:** None. **B. Gunter:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.14/Y14

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

Support: Oklahoma State University

Title: Exploring the Pharmacodynamic Properties of Fentanyl: A Comparative Analysis of Intraperitoneal Injection and Vapor Self-Administration in a Mouse Model of Substance Use Disorders

Authors: *S. BOBKOVA[1], M. HOCHSTETLER[1], B. CURRY[1], C. T. WERNER[2], C. W. STEVENS[1];
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Abstract: Abstract:
Amidst the ongoing opioid crisis, there is a critical need for research to comprehend the underlying mechanisms of substance use disorders and investigate potential treatments. While intravenous fentanyl administration stands as a gold standard in mouse studies, it presents challenges such as difficulty in placing catheters in mice and frequent catheter failure, hindering experimental progress. This study introduces an innovative vapor self-administration model for fentanyl delivery, aiming to evaluate the pharmacodynamic properties of fentanyl when administered passively through vapor. Methods:A series of experiments were conducted involving three groups of mice: intraperitoneal injection of fentanyl, passive vapor self-

administration using equivalent doses, and a control group for each experimental group. The analgesic effect of fentanyl was assessed through the hot plate test over a period ranging from 5 to 120 minutes. Mice were placed on a hot plate, and specific signs were evaluated within a 30-second window following fentanyl administration. Results:The analgesic effect of fentanyl was examined using the hot plate test, and a dose-response curve was constructed, revealing comparable analgesic responses in mice for both intraperitoneal injection and passive vapor self-administration of fentanyl. Conclusions:Utilizing the vapor self-administration model represents a promising advancement in the field research of substance use disorders. Our data sheds light on this method from a pharmacological perspective, demonstrating a robust analgesic effect of fentanyl through vapor self-administration, comparable to intraperitoneal administration.

Disclosures: S. Bobkova: None. **M. Hochstetler:** None. **B. Curry:** None. **C.T. Werner:** None. **C.W. Stevens:** None.

Poster

PSTR492: Drug Delivery

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR492.15/Y15

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

Title: Exploiting intranasal delivery of covalently reversible semi-peptidic inhibitors of tmprss2 to combat sars-cov-2 brain infection

Authors: *S. FERKOVÁ[1], J. COTE[3], A. DÉSILETS[2], K. ASSOUVIE[2], G. LEMIEUX[2], U. FRÖHLICH[2], P.-L. BOUDREAULT[2], P. SARRET[4];
[1]Dept. of pharmacology and physiology, [2]Pharmacol. & Physiol., Univ. de Sherbrooke, Sherbrooke, QC, Canada; [3]Univ. de Sherbrooke (FMSS), Sherbrooke, QC, ; [4]Pharmacol. & Physiol., Univ. of Sherbrooke, Sherbrooke, QC, Canada

Abstract: COVID-19, an infectious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to a global pandemic with profound public health implications, including neurological manifestations such as hypoxic-ischemic damage, encephalopathy, and neuroinflammation with marked microgliosis, astrogliosis and immune cell infiltration. The type-II transmembrane serine protease (TMPRSS2) has been identified as the proteolytic driver of SARS-CoV-2 cleavage at S2′ (PTKR797↓), S1/S2 (RRAR685↓), and X/Y sites, enabling major conformational changes and exposure of the fusion peptide that mediates the fusion of the viral and host cell membranes. Its crucial role in viral activation and replication makes dysregulation of TMPRSS2 activity a highly effective host-directed therapeutic strategy to block SARS-CoV-2 infection, its variants, and future widespread TMPRSS2-dependent respiratory viruses. Here, we report on the drug discovery process which led to the development of a highly effective covalently reversible semi-peptidic inhibitor based on the autoproteolytic cleavage sequence (RQAR614↓VVGG) of matriptase, to which a carboxy-terminal serine trap was linked in the form of a ketobenzothiazole group. To evaluate the potency and selectivity of

these candidates, an *in vitro* enzymatic screening assay was first performed, followed by an *in cellulo* neutralization assay to capture the pseudo-viral inhibition activity of each compound in Calu-3 cells. Moreover, we propose to use non-invasive intranasal delivery of our lead candidate as a strategic route to prevent SARS-CoV-2 brain infection, which potentially occurs through the olfactory bulb and nerve, or through the glossopharyngeal and vagus nerves. We also discuss the biological suitability of our semi-peptidic compounds for rapid intranasal delivery to the brain, based on the recent identified localization of TMPRSS2 in brainstem neuronal and glial cells. We propose to further evaluate our antiviral candidates *in vivo* using a K18-hACE2 transgenic mouse model, mirroring the severe pathology of COVID-19 in humans. Taken together, we have demonstrated the concept of covalently reversible TMPRSS2 inhibitors having sub-nanomolar potency and shown their inhibitory capabilities against SARS-CoV-2 infection. Efforts are underway to further improve their PK/PD profile and provide the *in vivo* results required to support their clinical development.

Disclosures: S. Ferková: None. **J. Cote:** None. **A. Désilets:** None. **K. Assouvie:** None. **G. Lemieux:** None. **U. Fröhlich:** None. **P. Boudreault:** None. **P. Sarret:** None.

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR493.01/Y16

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 1RF1MH123206

Title: Open-source software for the analysis of laser scanning kymographs

Authors: *R. H. CUDMORE;
Physiol. and Membrane Biol., Univ. of California, Davis, CA

Abstract: Kymographs are used for a range of experiments including fluorescent functional reports for cell activity such as Ca^{2+} and voltage, measuring cell growth, cellular lengthening and shortening in muscle cells, and *in vivo* blood flow from arterioles, venules, and capillaries. Kymographs are a powerful analytical tool as repeated line scans can be acquired with high spatial and temporal precision at sub-micrometer resolution on the order of a millisecond, allowing fast processes such as action potentials and blood flow to be quantified. Given their utility, a growing number of algorithms have been developed for kymograph analysis. Yet, most available software tools require substantial programming experience. Here we present an extensible software suite for a wide range of kymograph analysis. This software is modular and consists of a scriptable computational engine that includes implementations of common kymograph analysis algorithms. Using this engine, we have developed an easy-to-use, cross platform desktop graphical user interface, effectively lowering the barrier for adoption by mere biologists. To test this software, we provide analysis of brain capillary blood flow and

fluorescent Ca^{2+} imaging from both smooth muscle cells and brain neurons. All code is open-source, written in Python, and integrates into our freely available whole-cell current clamp software, SanPy.

Disclosures: R.H. Cudmore: None.

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR493.02/Y17

Topic: I.07. Data Analysis and Statistics

Support: NIMH for SBIR Grant R44MH119989

Title: 3d light sheet quantification at scale - computational challenges and solutions

Authors: J. H. ZEITOUN[1], A. REKSOATMODJO[2], C. REDD[1], N. GUANZON[1], R. AZEVEDO[3], H. GREER[4], M. NIETHAMMER[5], M. M. MCCORMICK[6], S. P. GANDHI[7], D. G. WHEELER[8], ***P. CHEUNG**[9,1];
[1]Translucence Biosystems, Irvine, CA; [2]Translucence Biosystems, Irvine, NC; [3]UC Irvine, Irvine, CA; [4]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Computer Sci., UNC at Chapel Hill, Chapel Hill, NC; [6]Kitware, Inc, Clifton Park, NY; [7]Neurobio. and Behavior, Univ. of California, Irvine, CA; [8]Translucence Biosystems Inc, Irvine, CA; [9]Refactor BioSciences, SAN DIEGO, CA

Abstract: Recent advances in optical clearing and light sheet imaging have opened an exciting new avenue for brain-wide, cellular resolution immunostaining at the forefront of a dimensional shift from 2D to 3D histology. Traditional histological methods have been a mainstay of neuroscience research dating back more than 100 years. Yet, despite great advances in tissue labeling and imaging technology, until very recently imaging more than a few hundred microns into a tissue has required slicing and mounting on slides. When looking for read-outs of genetic or pharmacological manipulations that affect the entire brain, this traditional focused approach is lacking, forcing researchers to limit observations to brain regions of interest. Providing access to the intricate anatomy of the whole intact brain, tissue clearing offers neuroscientists unbiased and complete views of brain anatomy and function. This increase in data creates challenges in converting this data into useful information. From data acquisition to brain region quantification, the traditional problems magnify when dealing with large data volumes. A single well-designed experiment yields terabytes of data. This poster describes several challenges encountered and the methodologies employed to overcome them. 1) Image Acquisition - we review Stitchy, a user-friendly software designed for tiling and stitching terabyte-scale light sheet images, addressing the complexities of large-scale imaging data. 2) Brain Registration / Alignment - we present a novel approach for tissue alignment/registration, which involves generating custom lightsheet templates from autofluorescence volumes and utilizing the ConstrICON registration method for

precise alignment to the Allen Brain Atlas. 3) Machine Learning workflows -- we compare traditional and deep learning methods for object classification/quantification and discuss the criteria for selecting the appropriate training workflow. 4) Visualization and reporting - we explore approaches for rapid visualization of large datasets, overcoming large data limitations faced by tools like ImageJ. Finally, we review the challenges associated with complex multi-day jobs that generate large sets of data and data types. 5) Workflow Design -- we present a drag and drop user interface that enables scientists to build complex workflows without code. 6) Job Scheduling and Compute Management - we review a Kubernetes-based architecture that enables diverse workflow jobs to scale and run across multiple machines over multiple days. 7) Data Management - we discuss database-centric approaches for organizing job results and integration with other third-party tools.

Disclosures: J.H. Zeitoun: A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **A. Reksoatmodjo:** A. Employment/Salary (full or part-time):; Translucence Biosystems. F. Consulting Fees (e.g., advisory boards); Translucence Biosystems. **C. Redd:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **N. Guanzon:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **R. Azevedo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **H. Greer:** None. **M. Niethammer:** None. **M.M. McCormick:** A. Employment/Salary (full or part-time):; Kitware. **S.P. Gandhi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **D.G. Wheeler:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. **P. Cheung:** A. Employment/Salary (full or part-time):; Translucence Biosystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems. F. Consulting Fees (e.g., advisory boards); Translucence Biosystems.

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR493.03/Y18

Topic: I.07. Data Analysis and Statistics

Support: New Frontiers in Research Fund - NFRFT-2022-00051
Canada Research Chairs - CRC-2017-00016

Title: An open and automated workflow for pre-processing lightsheet microscopy datasets employing the BIDS standard and the OME-Zarr next-generation file format

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Abstract: Lightsheet microscopy is gaining popularity for whole brain microscopy, however, major computational challenges remain, especially when applied in high-throughput settings. The Brain Imaging Data Structure (BIDS) specification is a data standard initially used to describe human neuroimaging datasets, but has since expanded to a wide range of modalities, including microscopy. The standard has led to the proliferation of BIDS Apps, containerized pipelines that are portable and easy to run because they understand BIDS datasets. BIDS now also makes use of the next-generation file format for microscopy, OME-Zarr, enabling chunk-based parallelization and cloud-optimized storage. We present here an open and automated workflow, SPIMprep, for transforming raw lightsheet images into BIDS microscopy datasets. SPIMprep is implemented in Python using the Snakemake workflow management system. It performs metadata extraction, flatfield correction (BaSiC), and stitching (BigStitcher), followed by the creation of a final validated BIDS dataset. The workflow is installed via pip, and the required container dependency is downloaded automatically by Snakemake. Input datasets are configured using a TSV file, specifying subject identifiers and paths to folders/archives containing the raw TIF files, and a YAML file is used to customize workflow configuration. The workflow can be executed in parallel on any local, cluster or cloud resources, and each step is also internally parallelized (Dask), taking advantage of the parallelization afforded by the chunked file format. The workflow can optionally write directly to cloud storage, facilitating data sharing and interoperability with existing web-based viewers. The workflow was evaluated on locally-acquired images of optically-cleared mouse brains, with 2 channels (autofluorescence, amyloid beta), 3x3 tiles, each 2160x2560 at 2.7um per pixel. Low and high-resolution (100um/4um) z-stacks were acquired, with 67/1,621 slices respectively. The end-to-end processing took 39 and 482 minutes respectively for low and high-resolution datasets, using a compute node with 32 cores and 128GB memory. In comparison, analogous processing performed outside the workflow took at least 24 hours, with our gains in efficiency due to parallel reads and writes enabled by Zarr. In summary, SPIMprep enables automated and high-throughput generation of lightsheet microscopy datasets in a portable and extensible framework. Leveraging OME-Zarr and BIDS, it paves the way for seamless data sharing and analysis. Future work includes developing BIDS Apps for cell-based quantification, atlas registration, and multi-modal integration.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Program #/Poster #: PSTR493.04/Y19

Topic: I.07. Data Analysis and Statistics

Title: Clearmap2.2 for the analysis of 3D whole brain optical images offers improved performance, co-localization analysis, tractographic mapping and new atlases support.

Authors: *C. V. ROUSSEAU[1], A. VIEITES-PRADO[1], E. DE LAUNOIT[2], E. DOUMAZANE[1], S. SKRIABINE[1], C. KIRST[3], N. RENIER[1];
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Abstract: Whole-brain optical-imaging techniques using light sheet microscopy and tissue clearing have revolutionized neuroanatomical studies by streamlining the obtention of single-cell resolution data of the entire central nervous system. These techniques, such as DISCO-based methods, offer the possibility to perform intact brain immunolabelings, in-situ hybridization, viral tracing, immediate early genes expression mapping, vascular mapping and tractographic reconstructions. However, analysing even standardized whole brain acquisitions is still the bottleneck of 3D neuroanatomical studies. The open-source ClearMap software has been pivotal in facilitating the reconstruction, processing, analysis, and visualization of these complex datasets, owing to its optimization towards handling terabyte-scale datasets. Here, we introduce the latest enhancements in ClearMap 2.2, focusing on simplified installation, an intuitive user interface with comprehensive documentation and visualization tools, and improved batch analysis capabilities. We also present custom and open-source developmental atlases fully integrated in the software and landmark-based registration. The updated pipelines offer greater versatility, accommodating an increasing number of file formats, arbitrary channel numbers and data-dependent interfaces (including co-localization analysis), along with improved vasculature postprocessing. Finally, enhanced parallelism, including hierarchical parallelism, optimizes computing resource utilization during data processing and allows, with novel algorithms, the extraction and tracing of fiber and graph-like structures. This enables the capture and quantification of non-resolvable geometrical features at the mesoscale, unlocking valuable information within complex biological networks.

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Poster

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Topic: I.07. Data Analysis and Statistics

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology.

Title: Characterizing subtypes of projecting axons in mice using topological data analysis and machine learning

Authors: *K. KURBAN[1,2], L. POLLINA[3], L. KANARI[2];
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Abstract: Persistent homology has emerged as a powerful tool in neuroscience for capturing the complex geometric and topological information of neuronal structures. However, these analyses were usually limited to the dendritic domain, due to the lower quality of staining in axons and incomplete reconstructions. Recently, advancements in fluorescent protein-based imaging techniques (Peng et al., 2021; Economo et al., 2016) have enabled the comprehensive reconstruction of entire neuronal morphologies, including both dendrites and axons. These datasets demonstrated that axonal reconstructions can vary significantly given a similar dendrite structure (Economo et al 2016., Qiu et al 2024). In our study, we exploited persistent homology to investigate the morphological heterogeneity within broadly labeled projecting axons of mice, using high-quality and atlas-registered data from the MouseLight project and metadata from Neuromorpho (Ascoli et al 2007). We first analyzed the axonal trees to generate persistent diagrams that were vectorized as 2d persistence images using path and Euclidean distances, which were then used as inputs to a dimensionality reduction algorithm (t-SNE). The subsequent 2d map is then clustered using unsupervised clustering algorithms (Gaussian Mixture Model and Density-Based Spatial Clustering of Applications with Noise i.e. DBSCAN). Our findings reveal the existence of distinct morphological subclusters of projecting axons, suggesting potential subtypes that are distinct from their broader categorization. We employed several morphological features to validate the statistical differences between these clusters, thereby illustrating the morphological diversity across these axonal subtypes. This approach not only improves the understanding of morphological classification through axonal projections but also enables more precise neuroanatomical classifications using a combination of topology and machine learning techniques in future studies.

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Poster

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Program #/Poster #: PSTR493.06/Y21

Topic: I.07. Data Analysis and Statistics

Title: Gene therapy in the central nervous system: ImageJ as a tool for image analysis

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Abstract: The axons of neurons are very long and can be injured easily. Damaged axons can't regenerate on their own in the central nervous system (CNS). To enhance the regenerative ability of axons and/or to increase the survival of damaged neurons, gene therapy has been considered as a potential technique. In this study, I explored ImageJ as an image analysis tool to interpret gene therapy experiment results. The image analysis was performed by the author, and the experimental data was provided by staff from the course 'Regenerative Neurobiology and Gene Therapy' at Cambridge Centre for International Research. Here, I used 3 image analysis techniques on ImageJ, including changing image format, counting measurement, and fluorescent intensity measurement. With the changing image format technique, a stack of images of a neuron taken by a microscope could be reformatted to give a better view of the neuron. Also, to test the effectiveness of the gene therapy in CNS between each treatment, the number of surviving cells could be counted using the counting measurement method. Finally, by using the fluorescence intensity analysis technique, I could observe how well AAV5- and AAV1-delivered green fluorescent protein (GFP) could be visualized in ImageJ. Results of the analysis of the experimental data showed that AAV1-delivered GFP was more effectively visualized by ImageJ than AAV5, and the counting measurement method can be used as a tool to test gene therapies that aim to improve axons regeneration. These results suggest ImageJ is a powerful tool for examining the effectiveness of gene therapy for the repair of axons. Since gene therapy is a fairly new field, ImageJ could further assist in the development of it by the analysis of images. More plugins and functions could be developed to help researchers in reformatting images taken by microscope and better accuracy in cell counting.

Disclosures: Y. Nguyen: None.

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Program #/Poster #: PSTR493.07/Y22

Topic: I.07. Data Analysis and Statistics

Title: Flexible automated platform for multimodal image-based neurite outgrowth analysis

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Abstract: Automated image-based analysis is an essential element of scalable strategies to accelerate neurobiology research. Image-based neurite outgrowth assays capture a complex

series of critical molecular and phenotypic events relevant for in vitro cell-based evaluations across multiple research areas, including neurotoxicity and neurodegeneration. Approachable benchtop automation provides an accessible solution for increasing throughput and reproducibility for neurite outgrowth assays in both academic and industrial laboratory settings. Here we have developed an automated instrument and software platform to enable high-throughput, multimodal neuron culture analysis that supports neurite outgrowth evaluations across time scales and assay methods. Neurite outgrowth analysis of iPSC-derived neuron cultures was investigated through fully automated label-free kinetic assays using a Agilent BioTek BioSpa8 incubator and Cytation imaging reader. Automated label-based fluorescence outgrowth assays, including end-point multichannel antibody-based analysis is also presented for both iPSC-derived and primary mouse cortical cultures. Results indicated that dose-response, response onset timing, and viability evaluations enabled specific, sensitive measurements of treatment effects across multiple phenotypic parameters important for neuron culture characterization, including neurite length and branching. Culture treatment with small molecules demonstrated enhancement or inhibition of neurite outgrowth based on quantitative IC/EC_{50} evaluations for both iPSC-derived and primary mouse neuronal cultures. This combination of automated benchtop instrument and software capabilities provides an approachable and flexible system for multimodal neurite outgrowth analysis to enable scale and reproducibility in neuronal model investigations. The neurite outgrowth analysis capabilities reported here complement existing system functionality that supports a broad range of neurobiology applications, including detailed characterization of 3D samples using confocal imaging approaches.

Disclosures: R. Mongeon: A. Employment/Salary (full or part-time):; Agilent Technologies, Inc. **S. Guadiana:** A. Employment/Salary (full or part-time):; Agilent Technologies, Inc. **J. Clayton:** A. Employment/Salary (full or part-time):; Agilent Technologies, Inc..

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Program #/Poster #: PSTR493.08/Y23

Topic: I.07. Data Analysis and Statistics

Title: Jumping dimensions: Integration of multimodal imaging into a unified brain atlas space

Authors: *S. NAGY[1], J. PERENS[1], A. PARRA ACERO[1], J. LERCKE SKYTTE[1], J. HECKSHER-SØRENSEN[2];
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Abstract: The intricate nature of the mammalian brain necessitates advanced methodologies for comprehensive analysis to elucidate its function and pathophysiology. Here, we present an innovative pipeline for integrating diverse imaging modalities into a unified brain atlas space, aiming to enhance understanding of neurobiology, and accelerating drug development for CNS disorders.

Recent advancements in 3D imaging, notably light-sheet fluorescence microscopy (LSFM) combined with tissue-clearing techniques, have enabled detailed examination of intact biological specimens, including the brain. Leveraging our reference mouse brain atlas for spatial registration, we have established a standardized framework for unbiased analysis of 3D imaging data, facilitating the extraction of quantitative information such as gene expression profiles and cell counts.
In addition to 3D imaging, the integration of complementary 2D experimental data, including histopathology, in situ hybridization, and spatial transcriptomics, will become essential for understanding the underlying biology of the brain and supporting hypothesis-driven drug discovery. This integration would allow the exploration of cellular interactions and molecular pathways underlying neurological conditions, surpassing the limitations of individual data streams, and providing a versatile toolbox for researchers.
Our approach involves seamlessly integrating data from various modalities into a unified atlas space of the mouse brain, allowing precise alignment, anatomical annotation and analysis at different scales and data types, ranging from single-cell gene expression to histological markers to global brain activity. By leveraging AI models, we aim to bridge the gap between 2D and 3D data, expanding the toolkit for understanding disease mechanisms and accelerating the discovery of potential therapeutic targets, addressing the urgent needs in CNS disorder research.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U01NS132158

Title: Cloud computing workflows and validation framework for smart scanning electron microscopy

Authors: *D. XENES[1], H. MARTINEZ[1], C. A. BISHOP[1], J. MATELSKY[1], I. S. CHANDOK[2], Y. LI[2], M. GUERRAOUI[3], Y. MEIROVITCH[2], S. SAWMYA[3], B. A. WESTER[1];
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Abstract: High-throughput connectomics, crucial for generating large-scale neural wiring diagrams, is currently limited to a few resource-rich institutes due to the prohibitive cost. New “SmartEM” technology can optimize the acquisition of image data by dynamically modulating

dwell time necessary to sufficiently acquire pixel-level data needed to generate high quality neural circuit reconstructions. These optimizations have produced a 7-fold acceleration in image acquisition time. The resulting image data from this approach have a low base resolution and are fused with high resolution image data in areas most salient to high quality segmentation and generation of wiring diagrams.Here, we demonstrate that by using a scalable cloud-based infrastructure that can accept various algorithms into dockerized workflows, downstream image processing steps such as stitching, alignment, membrane detection, and segmentation can keep pace with accelerated image production. We also demonstrate algorithms which can perform these tasks on images with heterogeneous resolutions. Lastly, we leverage a modular and robust validation framework to assess the neural circuit reconstruction pipeline and accuracy of generated wiring diagrams via several key metrics (e.g., synapse precision/recall/f1, large-scale graph analysis, run length). This framework is used for performance tuning of the intelligent imaging system and downstream data processing steps. We will release these tools for the larger community to improve data collection and processing methods.With this cloud-based workflow and validation framework, we increase the speed at which connectomic datasets can be produced while mitigating any loss of quality.

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Poster

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Topic: I.07. Data Analysis and Statistics

Support: NIH UM1NS132250
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Title: From networks to inference: using graph theory to characterize connectome reconstruction quality in nanoconnectomes

Authors: P. RATHI[1], J. BROWN[1], P. K. RIVLIN[2], ***W. GRAY RONCAL**[3];
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Abstract: The field of nanoconnectomics aims to map the brain's networks at the level of individual neurons and their synaptic connections. The field is continuously advancing, characterized by ongoing efforts to incorporate new technologies and algorithms to reconstruct brain wiring. Despite significant breakthroughs, persistent challenges related to reconstruction assessment, error identification, and variability across datasets remain formidable obstacles. Our objective is to develop a toolkit that leverages existing proofread datasets and graph analysis

methodologies to understand the error characteristics of an unknown graph. We will use proofread examples from worm, fly, and mouse brains to assess networks based on fundamental properties and topological attributes (e.g., loops, path length, communities), emphasizing features relevant to network neuroscience. Features derived from gold-standard graphs will be compared to those generated from example perturbations, thereby providing a greater understanding of how features characterize graph quality. We believe that these results will help the community more rapidly understand graph errors, reliably perform inference tasks, and enable faster, more reliable discoveries.

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Poster

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Topic: I.07. Data Analysis and Statistics

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Title: DrosoGPT: a natural language querying interface for exploring the structure and functional logic of the Drosophila brain

Authors: *P. DEEVI[1], Y. ZHOU[2], S. SHUKLA[1], B. BU[1], A. A. LAZAR[1];
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Abstract: Understanding the activity and connectivity data of Drosophila neural circuits can provide valuable insights into their functional logic. Analyzing even small circuits requires manually sifting through vast amounts of literature and running numerous scripts, which can be error-prone and labor-intensive.Tools such as NeuroNLP++ [1] aim to simplify the exploration of connectomic data using only natural language queries. Due to the rule-based English query interface, prompts currently cannot handle complex queries and are limited to only basic neuron and synaptic information. There is a critical need to seamlessly integrate neural circuit activity data with connectomic data and provide large language model tools for their exploration.
We developed DrosoGPT, an open-source tool based on a large language model (LLM) designed to provide Drosophila researchers with a unified natural language interface for rapid and comprehensive connectome analysis. DrosoGPT provides two main capabilities: 1) visualizing connectome/synaptome data in response to complex English queries, free of specific rules imposed in current NeuroNLP;2) providing an intuitive ChatGPT-like interface to query about the Drosophila brain in the worldwide literature, bridging the knowledge of functional logic with the connectome/synaptome data.For example, a query ``show a patchy LN of the antennal lobe that receives at least 40 inputs from DM4 OSN, color it in red, and color the LN's output synapses to PNs colored by glomeruli" prompts DrosoGPT to query for and visualize the

neurons/synapses of interest as specified.It also provides the connectivity matrix and synapse distributions, retrieves comprehensive literature information on the neuron, and allows further inquiries about this neuron type.To support these capabilities, we pre-trained an LLM on a common repository linking connectome data, literature of over 800 olfaction papers, and the Drosophila Anatomy Ontology. It is further fine-tuned to generate NeuroArch database [2] queries in Python to resolve complex connectome/synaptome queries.
DrosoGPT offers a singular solution to seamlessly analyze neuroanatomy data across modalities, enabling efficient exploration of the functional logic of neuron circuits.Our new research methodology built on DrosoGPT substantially simplifies access to complex datasets, greatly accelerating connectomics-based research for Drosophila and other model organisms.
[1] Lazar, Turkcan \& Zhou (2022) Front. Neuroinform. 16:853098.
[2] Ukani et al. (2019) bioRxiv. DOI: 10.1101/580290v1

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Poster

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Title: Modeling spatial transcriptomics experiments within the BICAN consortium

Authors: *P. M. BAKER[1], L. ERION BARNER[4], M. KENNEY[5], M. KUNST[2], B. R. LONG[7], L. NG[7], B. REN[9], A. J. ROPELEWSKI[6], R. SANCHEZ[8], S. C. SEEMAN[3], K. A. SMITH[3], Q. ZHU[10], C. L. THOMPSON[3];
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Abstract: The Brain Initiative Cell Atlas Network (BICAN) is a consortium for constructing large scale atlases of cell types in the brain across multiple species (human, mouse, NHP) and developmental stages. Spatial transcriptomic techniques used in BICAN, including MERSCOPE, Xenium, Stereo-seq, DBit-Seq and Slide-Tags, are central to our efforts to allow the combined precision of spatial localization and transcriptomic targeting of cell types that are critical for this

work. Spatial transcriptomic datasets can pose challenges for data management. The large size and distributed nature of imaging datasets is a challenge for data sharing and reuse, requiring the standardization of data organization, metadata, and analysis pipelines and workflows for resource management. The increasing variety of platforms that are used to generate spatial transcriptomics data differ in organization of data and the metadata collected in experiments, posing additional challenges for data standardization efforts. It is also critical to standardize the metadata collected describing the gene panels and probes used for targeting cell types in these experiments for interpretability and replicability of results. To address these issues, we formed a working group to develop standards for spatial transcriptomics experiments. In our first phase we drafted specifications for imaging-based methods. We performed user surveys with our members to determine the critical use cases for data sharing, analysis, visualization, and reuse. We also met with scientists to detail their tissue dissection plans. Our scientists created a draft data model of workflows from tissue preparation through to data outputs and analysis, with the goal of capturing essential steps and processes common across techniques and platforms. We then developed a standard set of metadata fields essential for covering our key use cases, as well as fields for data cataloging and archiving within the BICAN data ecosystem that will enable sharing and search for the broader community. The complete data model has been implemented in LinkML for incorporation into the BICAN Knowledge Base. In addition to this work within BICAN, we have been reaching out to align our efforts with external consortia (HuBMAP, SSPsyGene). We continue to refine our data model and metadata to address novel uses and facilitate use of this data for combining spatial transcriptomic and single-cell omics datasets across BICAN. The data model will also be used in the development of tools that can be used with all of our spatial transcriptomics datasets for visualization and search through the BICAN data catalog, as we have demonstrated for the Allen Institute ABC Atlas.

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Poster

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Topic: I.07. Data Analysis and Statistics

Support: NIH Grant RF1MH133777

Title: A scalable cloud-based framework for multi-modal neuronal cell type mapping

Authors: Y. XU, S. VELASQUEZ, J. CHANG, B. WANG, M. LEWIS, E. WEITZ, A. HAESSLY, J. BISTLINE, B. HILL, S. FLEMING, Y. ORDABAYEV, J. KITONYO, M.

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Abstract: Categorizing neurons into different cell types has been a classical approach to understanding the brain. While efforts have been made to reconcile across different neuron characterization approaches, most criteria are fundamentally subjective, and often rely on manual annotation. In this project, we set out to solve the cell type classification problem by developing state-of-the-art machine learning methods with a cascade approach. We demonstrate that by framing “multimodal data integration” as the “cross-modal similarity-based (semantic) search” problem, we break the modality barrier: given a single-cell measurement in one modality, we identify similar cells across a large collection of datasets, measured either in the same or different modalities. Another core mission of this project is to unlock the potential of newly developed and existing resources in the BRAIN Initiative by making them widely available and reusable. To enable FAIR data access, data integration tools, and broadly accessible results, we are building a cloud framework integrated with the BRAIN Initiative ecosystem. In this framework, the machine learning tools will be deployed in the BICCN/BICAN cloud workbench, Terra, and made accessible to the general scientific community. We have developed solutions for streaming data from the federated BRAIN Initiative data repositories, including NeMO, DANDI, and BIL, so that single neuron data from multiple sources can be co-analyzed within the same workspace. We also extend the capability of Single Cell Portal, a BICCN/BICAN visualization platform, to facilitate exploration and scientific discovery. Using a globally available computing workbench that can access data from federated repositories creates a space where scientists from different institutions and communities can collaborate and share data and methodology with minimal technical barriers and without the assumption of maintaining local institutional resources only available to the most wealthy of institutes. Going forward, we will provide training materials such as workshops to onboard researchers to these cloud resources and facilitate scientific implementation.

Disclosures: B. Huo: None.

Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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NSF Grant ACI-1445606
NSF Genat ACI-1928147

Title: The Brain Image Library: New features for enhanced data integration, accessibility, and visualization

Authors: M. KENNEY[1], I. CAO-BERG[1], L. TUITE[1], R. LAGHAEI[1], K. HE[2], I. VASYLIEVA[2], A. M. WATSON[2], *A. ROPELEWSKI[1];
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Abstract: The Brain Image Library (BIL) is the centralized repository of brain microscopy data. BIL provides access to a diverse range of whole-brain microscopy image datasets, along with secondary data such as neuron morphologies, connectivity between cells, spatial transcriptomics, and historical collections of significant value to the community. BIL welcomes contributions of microscopy data relevant to the BRAIN Initiative, including data from primates, most mammals, and model organisms.
One core mission of the Brain Image Library is to utilize available computing resources to make data easily visualizable. We are developing an on-demand transformer, BrAinPI, to optimize the accessibility and reuse of the diverse datasets at BIL. This will facilitate the delivery of data in various formats and provide flexibility to the neuroscience community. This tool is already serving our Neuroglancer data viewer, and is compatible with visualization tools like Napari or Neuroglancer. Using the Neuroglancer data viewer at BIL, users can visualize petascale datasets even on a smartphone, at the speed of mobile internet, without registration or downloading data. Additionally, we are developing a way to easily visualize 2D histology data in a browser as high-resolution zoomable images using a lightweight OpenSeaDragon viewer. Lastly, we have developed a plugin for napari called napari-bil-data-viewer that enables users to visualize publicly available datasets at BIL over the web without registration and is pre-loaded with a comprehensive set of downsampled whole brain fMOST datasets and associated neuron tracing files.
Here, we will also present new metadata features at BIL including a new metadata schema for spatial transcriptomics data to increase the reusability of such data and provide a better description of these data in BIL. We have also developed a Metadata API and web portal that enables full-text searching or searching of individual metadata fields. These tools significantly enhance the accessibility, findability, and reusability of data at BIL. As a whole, BIL's computational, visualization, and metadata tools aim to empower the neuroscience community by providing a user-friendly platform for utilizing a wide range of imaging datasets.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

Location: MCP Hall A

Time: Wednesday, October 9, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR493.15/Y30

Topic: I.07. Data Analysis and Statistics

Support: NIMH Grant 1U24MH130918-01

Title: Enhancing querying, integration, and exploration of brain cell types through combining knowledge graphs and GenAI

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Abstract: The Allen Institute's Brain Knowledge Platform aims to allow neuroscientists worldwide to explore, understand, and interpret the vast corpus of mammalian brain data from the Allen Institute and community consortia. Answering fundamental questions about brain anatomy and cell types requires unifying disparate analyses and data streams. Functionality studies must be compared to data-driven cell types derived from any number of experimental methods in the context of anatomical dissections across multiple species with complicated ortholog and homolog relationships between them. Modeling these datasets and navigating them in a useful way is daunting for tabular databases. We solve this problem with the Allen Brain Knowledge Graph, which provides neuroscientists a simple, intuitive web experience to browse and search brain cell types, anatomy, and genes across datasets and species. The Allen Brain Knowledge Graph combines the power of knowledge graphs with GenAI to explore complex datasets at a granular level, comparing data-driven results with historical knowledge and finding patterns previously hidden by the complexity of the datasets. The Allen Brain Knowledge Graph models full datasets in a graph that relates cell types, anatomical structures, genes, cells, and more. Each entity takes whatever shape is necessary to represent its contents. The connections between entities are modeled by well-schematized relationships. Efficient querying is achieved by selecting an entity of interest, returning every relationship connecting to that entity, and finally returning every entity mentioned by those relationships. Users explore the interconnectedness of the data by re-centering the query on one of the returned entities. Search is further optimized by asking a Large Language Model to summarize each datum and ingesting the resulting summaries into an instance of OpenSearch, a text-search tool that allows users to query data according to its similarity to an arbitrary human language query. We populated our prototype knowledge graph with transcriptomic cell type taxonomies from recent whole mouse brain (Yao et al. 2023) and whole human brain (Siletti et al. 2023) studies. These taxonomies are supplemented by spatial distributions from spatial transcriptomic studies, classifications according to general brain and cellular biological ontologies, and expert annotations denoting ortholog relationships across species. This work is supported by National Institute of Mental Health award number 1U24MH130918-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Topic: I.07. Data Analysis and Statistics

Support: NIH U24MH130919
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Title: Bican metadata, modeling, and ontology management

Authors: *P. RAY[1], P. M. BAKER[2], S. NADENDLA[3], M. GIGLIO[4], D. JARECKA[5], K. SMITH[1], M. KENNEY[6], P. TRIVEDI[5], T. FLISS[1], P. BISHWAKARMA[1], M. E. MARTONE[7], S. S. GHOSH[8], L. NG[1], C. L. THOMPSON[1];
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Abstract: Through the BICCN and BICAN, scientists have generated large, high-quality datasets for cell type classification using a range of single-cell transcriptomic and epigenomic techniques. These datasets provide a vast amount of information but without detailed metadata and provenance, it can be challenging to integrate the data into a coherent system. Additionally, reuse of this data requires standardization of and accessibility to the data in its various locations and archives. Large consortia work requires additional coordination and alignment beyond what is needed at a smaller scale. Labs and data centers may employ SOPs or protocols that are well-known locally, but without transparency, openness, and a commitment to FAIR, it is likely that important information is lost in the process of integration. To mitigate these problems, the BICAN Metadata and Ontologies Integration Working Group has established a metadata standardization process wherein a scientific lab or group can standardize and publish their metadata records to harmonize with the wider BICAN consortium. Metadata schemas are validated via a Metadata Review Process, which, along with our Vocabulary Services technologies and tools (LinkML, PURL), provides a central service for harmonization of terms and definitions cross-consortium and ensures consistent data flow through the ecosystem. This provides researchers and the community a suite of tools for data integration and supports the BICAN data ecosystem. Once the metadata schemas are standardized, they are versioned and published. Once published, an accompanying data model (LinkML) is created for each version of the metadata schema. Once a metadata schema and model are created, we create additional standard references in our application ontology (BICANO) that describe entities to help scientists communicate about experiments and results. BICANO includes methods, techniques, tools, protocols, specimens, samples, and more. Entities of interest outside the BICAN consortium are marked for inclusion in standard reference ontologies and shepherded to those ontologies. This allows us to link related entities and map data across techniques, modalities, species, developmental stages, and anatomy. This process of standardization and FAIRification provides scientific value for reproducibility, technological value through implementation in knowledge

graphs, and organizational value through accurately indexing data and metadata. Future directions include harmonizing our efforts with related consortia, ensuring interoperability of data models with global efforts, and extending a framework for a knowledge graph.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Topic: I.07. Data Analysis and Statistics

Support: NIH 1U24MH130918-01

Title: Using the LinkML ecosystem for creating BICAN data model

Authors: *D. JARECKA[1,2], P. TRIVEDI[3], P. M. BAKER[4], A. A. BHANDIWAD[4], P. BISHWAKARMA[4], T. CHHETRI[3], S. DANIEL[4], N. DEHGHANI[3], T. FLISS[4], P. RAY[4], K. A. SMITH[4], C. L. THOMPSON[4], L. NG[4], S. S. GHOSH[3];
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Abstract: The BRAIN Initiative Cell Atlas Network (BICAN) was established to create a comprehensive cellular atlas of the human brain and its relationship across atlases in other species. A key component of this effort is the development of a knowledge base and to make it openly accessible, comprehensible, and usable by researchers within and beyond the consortium. Given the increasing volume and complexity of the data, a special emphasis has been placed on machine readability and usability of the information by following the FAIR principles, i.e., enabling the Findability, Accessibility, Interoperability, and Reuse of digital assets and information. Developing a comprehensive data model to represent the experimental data and its provenance, which can be integrated with various technologies, is essential for connecting data with other sources of information to generate knowledge. In the BICAN project, a diverse array of entities and processes must be modeled that include donors of various species across lifespan, complex transcriptomic and other experimental pipelines, and information about genes, neuroanatomy, cell types, and atlases. Here we demonstrate the use of Linked Data Modeling Language (LinkML) ecosystem to develop the BICAN data models and a corresponding toolkit for interacting with data ingested into this information space. This comprehensive model includes definitions of biological and digital entities, chemical and digital processes, as well as an extensive set of metadata about each of them. The models are used to initialize a

comprehensive Python library that is used to ingest and structure data from genome annotation references, neuroanatomical atlases, and BICAN datasets. These data form the core of the knowledge base and are available and accessible for developing downstreaming applications.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Program #/Poster #: PSTR493.18/Z1

Topic: I.07. Data Analysis and Statistics

Title: Processing Challenging Large Scale Lightsheet Datasets for Whole Brain Axon Imaging and MFISH

Authors: *S. SESHAMANI[1], G. KOVACS[1], C. ARSHADI[1], C. BERRY[1], C. LAITON[2], S. MCCULLOCH[1], M. E. GARRETT[3], A. GLASER[1], J. V. CHANDRASHEKAR[1], K. SVOBODA[4], D. FENG[1], C. BERRY[1];
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Abstract: Recent advances in tissue clearing, tissue expansion and light-sheet imaging enable new ways to collect data that can enable examination of multi-regional circuits throughout the brain, visualization of the complete morphology of neurons within these circuits, and linking the intact neurons with their molecular identity through spatial transcriptomics. At the Allen institute for Neural Dynamics we aim to develop a shared data resource for the neuroscience community that can enable such studies. For this, we have set up two lightsheet imaging platforms: 1) ExA-SPIM imaging of whole mouse brains that are sparsely labelled and expanded approximately 3x, and 2) multiplexed FISH (mFISH) on subvolumes of tissues. Raw images (tiles) collected from these light-sheet microscopes must be processed in order to render them into coherent volumes and extract relevant information from them. We are developing cloud-based pipelines for processing data from both setups. These pipelines involve some common steps: metadata generation, image compression, cloud upload, tile-to-tile registration and fusion for volume generation. Further, for ExA-SPIM data, we perform microscope specific intensity correction, segmentation of neuron bodies, and registration to the CCF Atlas. For the mFISH data, we perform microscope specific distortion correction, cell segmentation, gene expression spot counting across multiple channels, and round to round registration. Several of the algorithms we use have been developed for smaller scale datasets. However, the scale of data that we collect presents great challenges for standardized, efficient data processing (ExA-SPIM data ~100TB/volume and MFISH data on the order of ~200 GB/round) as well as challenges in

validation. This poster describes the advances that we have made towards a cohesive cloud based workflow with each of these steps strung together for large scale image processing We also discuss tools that we have developed for visual as well as quantitative validation. The raw data, code and pipeline outputs for each dataset are openly accessible, accompanied with metadata for each of the image processing steps. This commitment to fair, open and reproducible science ensures that our resources serve as valuable assets for the research community.

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Poster

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Program #/Poster #: PSTR493.19/Z2

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U01MH130907

Title: An open, version-controlled, modular, and cloud-based analysis pipeline for processing calcium imaging data, available for widespread use

Authors: *A. LEON[1], J. FRIEDRICH[2], M. DAVIS[2], J. KIM[2], J. LECOQ[3], K. DAIE[4], J. YOUNG[2], S. E. DE VRIES[2], M. E. GARRETT[5], D. FENG[2];
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Abstract: Optical imaging methods using fluorescent calcium indicators are routinely employed to observe the spiking activity of large neuronal populations. Imaging experiments yield vast datasets (2.5GB/min) that require processing to extract neuronal activity, presenting challenges of scalability and data provenance.We present a modular pipeline that performs motion correction, multiplane signal decrosstalk, cell segmentation, trace extraction, normalization with baseline correction (dF/F), and event detection. We leverage the Code Ocean platform to build a NextFlow workflow that runs each process, contained in a Docker environment, on AWS for high throughput processing (up to eight datasets per day at 200GB each). We have built public repositories on GitHub for each capsule from motion correction through event detection to process single-plane and multiplane calcium imaging configurations. Our approach combines community-based open-source tools (Suite2p; Pachitariu et al., 2016. CaImAn; Giovannucci et al., 2019) alongside custom solutions, incorporating quality control at each step of data processing. We integrate various published methods, such as deep learning (e.g. Cellpose; Stringer et al. 2020) or matrix factorization (e.g. CNMF; Pnevmatikakis et al., 2016) for cell-identification, and non-negative deconvolution (e.g. OASIS; Friedrich et al. 2017) or supervised

deep networks (e.g. CASCADE; Rupprecht et al. 2021) for spike inference.Our modular approach facilitates method interchangeability and end-to-end pipeline evaluation, capturing interdependencies between processing steps usually assessed in isolation. We validate the pipeline on data annotated by human labelers, realistic simulations using NAOMi (Song et al., 2021), and simultaneous cell-attached recordings and two-photon imaging of GCaMP8 and 7 (Rózsa et al., 2023). We use annotated and simulated data to assess cell segmentation, balancing detecting a large quantity of cells with accurately extracting neural activity traces. We compare inferred spike rates with ground truth from simulation or electrophysiological recordings to ensure quality.The integration of these techniques and our openly available data processing pipeline serve as a resource to support large-scale processing of calcium imaging data. The accompanying evaluation pipeline and ground truth data serve as a test bed for evaluating existing and future algorithmic improvements.

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Poster

PSTR493: Software Tools: Imaging, Anatomy, and Connections

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Program #/Poster #: PSTR493.20/Z3

Topic: I.07. Data Analysis and Statistics

Title: Microscopy to Knowledge: An Automated Cloud Processing Pipeline for Mesoscale Neuroanatomy

Authors: *C. LAITON[1], N. LUSK[2], D. WANG[1], M. TAORMINA[2], M. T. SUMMERS[1], J. ROHDE[1], Y. I. BROWNING[1], G. F. LYNCH[1], K. SVOBODA[1], D. FENG[1], S. SESHAMANI[1]; [1]Neural Dynamics, [2]Brain Sci., Allen Inst., Seattle, WA

Abstract: Selective Plane Illumination Microscopy (SPIM) microscopy is widely used for high-resolution imaging of brain tissue, including whole mouse brains. SPIM is routinely used to map fluorescently labeled mRNA, proteins, and neurons across the brain. Advances in imaging speed now allow rapid imaging of entire brains and experiments across a wide range of conditions. These experiments produce huge data volumes and thus create challenges in data management and processing. To address these challenges, we have developed an end-to-end automated cloud processing pipeline to extract the locations of neurons labeled with fluorescent proteins in the mouse brain.
Our pipeline leverages cloud computing, open-source tools, and cloud-friendly data formats (OME-Zarr) to manage large-scale microscopy data. Our data are cleared mouse brains imaged using the commercial SPIM microscope (SmartSPIM) at a 2.0 μm z step and an x-y pixel size of 1.8 μm. The pipeline consists of the following steps: 1) Metadata generation, image compression and fast upload to our cloud storage in Amazon Web Services; 2) image preprocessing, including

flat-field correction and de-striping; 3) stitching of individual tiles to generate a contiguous volume with TeraStitcher; 4) cell detection using cellfinder, a convolutional neural network based detector; 5) registration of the volume to to the standard mouse atlas Allen Common Coordinate Framework (CCF) with the Advance Normaliztion Tools package (ANTs). The output are the locations of detected cell bodies across the brain. Image volumes and analysis output can be visualized shared by URL using Neuroglancer. The turnaround time from data acquisition to quantification visualization is 21.8 hours. The pipeline was implemented as a fully open, containerized NextFlow pipeline using the Code Ocean cloud analytics platform. The raw data, code and pipeline outputs for each dataset are openly accessible, accompanied with metadata for each of the image processing steps. This commitment to fair, open and reproducible science ensures that our resources serve as valuable assets for the research community.

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